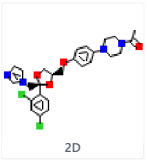
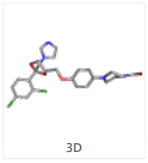
PubChem

COMPOUND SUMMARY

Ketoconazole

PubChem CID:	47576
Structure:	 2D  3D Find Similar Structures
Chemical Safety:	 Acute Toxic, Health Hazard, Environmental Hazard Laboratory Chemical Safety Summary (LCSS) Datasheet
Molecular Formula:	$C_{26}H_{28}Cl_2N_4O_4$
Chemical Names:	ketoconazole Panfungol Ketoisdin Orifungal M Nizoral More...
Molecular Weight:	531.4 g/mol
Dates:	Modify: 2019-07-22 Create: 2005-06-24

Ketoconazole is a synthetic derivative of phenylpiperazine with broad antifungal properties and potential antineoplastic activity. Ketoconazole inhibits sterol 14-a-dimethylase, a microsomal cytochrome P450-dependent enzyme, thereby disrupting synthesis of ergosterol, an important component of the fungal cell wall. (NCI04)

▸ from NCIt

Ketoconazole is an imidazole fungicidal agent with a very broad spectrum of activity against many fungal species that is used for treatment of superficial and systemic fungal infections. Ketoconazole is a well documented cause of clinically apparent acute drug induced liver injury and is no longer recommended as a first line antifungal agent.

▸ from LiverTox

(2S,4R)-ketoconazole is a cis-1-acetyl-4-(4-{[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy}phenyl)piperazine which dioxolane moiety has (2S,4R)-configuration. It is an enantiomer of a (2R,4S)-ketoconazole.

▸ from ChEBI

Cite Download

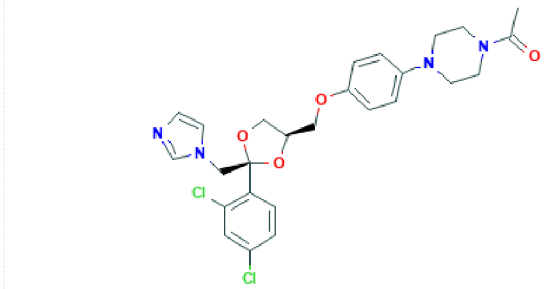
CONTENTS

1 Structures

1.1 2D Structure

Find Similar Structures Get Image Download

Chemical Structure Depiction



from PubChem

1.2 3D Conformer

from PubChem

2 Names and Identifiers

2.1 Computed Descriptors

2.1.1 IUPAC Name

1-[4-[4-[[(2*S*,4*R*)-2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]ethanone

from PubChem

2.1.2 InChI

InChI=1S/C26H28Cl2N4O4/c1-19(33)31-10-12-32(13-11-31)21-3-5-22(6-4-21)34-15-23-16-35-26(36-23,17-30-9-8-29-18-30)24-7-2-20(27)14-25(24)28/h2-9,14,18,23H,10-13,15-17H2,1H3/t23-,26-/m1/s1

from PubChem

2.1.3 InChI Key

XMAYWYJOQHXEEK-ZEQKJWHPSA-N

from PubChem

2.1.4 Canonical SMILES

CC(=O)N1CCN(CC1)C2=CC=C(C=C2)OCC3COC(O3)(CN4C=CN=C4)C5=C(C=C(C=C5)Cl)Cl

from PubChem

2.1.5 Isomeric SMILES

CC(=O)N1CCN(CC1)C2=CC=C(C=C2)OC[C@@H]3CO[C@@](O3)(CN4C=CN=C4)C5=C(C=C(C=C5)Cl)Cl

from PubChem

2.2 Molecular Formula

$C_{26}H_{28}Cl_2N_4O_4$

from ILO International Chemical Safety Cards (ICSC); PubChem

2.3 Other Identifiers

2.3.1 CAS

65277-42-1

from ChemIDplus; European Chemicals Agency (ECHA); Human Metabolome Database (HMDB); ILO International Chemical Safety Cards (ICSC); The National Institute for Occupational Safety and Health (NIOSH)

Other CAS

72093-26-6

from ChemIDplus

142128-57-2

from ChemIDplus; EPA DSSTox

142128-59-4

from ChemIDplus

2.3.2 EC Number

265-667-4

from European Chemicals Agency (ECHA)

2.3.3 ICSC Number

1700

from ILO International Chemical Safety Cards (ICSC)

2.3.4 RTECS Number

TK7912300

from The National Institute for Occupational Safety and Health (NIOSH)

2.3.5 UN Number

2811

from ILO International Chemical Safety Cards (ICSC)

2.3.6 UNII

2DJ8R0NT7K

from FDA/SPL Indexing Data

2.3.7 Wikipedia

(2S,4R)-ketoconazole

from Wikipedia

2.4 Synonyms

2.4.1 MeSH Entry Terms

Ketoconazole
Nizoral
R 41400

R-41400
R41,400
R41400

from MeSH

2.4.2 Depositor-Supplied Synonyms

ketoconazole	Ketoconazol	CHEBI:47518
Panfungol	Sebazole	1-acetyl-4-(4-{[(2S,4R)-2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan
Ketoisdin	Levoketoconazole	HSDB 7447
Orifungal M	COR-003	Brizoral
Nizoral	UNII-2DJ8R0NT7K	Teryzolin
Ketoderm	Ketoconazol [INN-Spanish]	Terzolin
(-)-Ketoconazole	Ketoconazolum [INN-Latin]	EINECS 265-667-4
Ketozole	142128-57-2	Onofin K
Normocort	Ketoconazole, (2S,4R)-	KW-1414
65277-42-1	2DJ8R0NT7K	BRN 4303081
Fungarest	Ketocanazole	(+-)-cis-1-acetyl-4-(p-((2-(2,4-dichlorophenyl)-2-(imidazol-1- ylmethyl)-1,3-dioxolan-4-
Fungoral	Ketoconazolum	1-[4-[4-[[(2S,4R)-2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]met
Nizoral a-D	CHEMBL295698	Piperazine, 1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxo

from PubChem

3 Chemical and Physical Properties

3.1 Computed Properties

Property Name	Property Value
Molecular Weight	531.4 g/mol
XLogP3	4.3
Hydrogen Bond Donor Count	0
Hydrogen Bond Acceptor Count	6
Rotatable Bond Count	7
Exact Mass	530.148761 g/mol
Monoisotopic Mass	530.148761 g/mol
Topological Polar Surface Area	69.1 A^2
Heavy Atom Count	36
Formal Charge	0
Complexity	735
Isotope Atom Count	0
Defined Atom Stereocenter Count	2
Undefined Atom Stereocenter Count	0
Defined Bond Stereocenter Count	0
Undefined Bond Stereocenter Count	0
Covalently-Bonded Unit Count	1
Compound Is Canonicalized	Yes

from PubChem

3.2 Experimental Properties

3.2.1 Physical Description

Solid

from Human Metabolome Database (HMDB)

COLOURLESS CRYSTALS OR POWDER.

from ILO International Chemical Safety Cards (ICSC)

3.2.2 Color/Form

Crystals from 4-methylpentanone

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Cambridge, UK: Royal Society of Chemistry, 2013., p. 983

from HSDB

3.2.3 Melting Point

146 deg C

Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 2191

from HSDB

146°C

PhysProp

from Human Metabolome Database (HMDB)

148-152 °C

from ILO International Chemical Safety Cards (ICSC)

3.2.4 Solubility

In water, 0.29 mg/L at 20 deg C (est)

US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.11. Nov, 2012. Available from, as of Aug 27, 2014: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm

from HSDB

0.0866 mg/L

from Human Metabolome Database (HMDB)

Solubility in water: none

from ILO International Chemical Safety Cards (ICSC)

3.2.5 Vapor Pressure

6.41X10-14 mm Hg at 25 deg C (est)

US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.11. Nov, 2012. Available from, as of Aug 27, 2014: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm

from HSDB

Vapor pressure, Pa at 25 °C: (negligible)

from ILO International Chemical Safety Cards (ICSC)

3.2.6 Octanol/Water Partition Coefficient

log Kow = 4.34

Hansch, C., Leo, A., D. Hoekman. Exploring QSAR - Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society., 1995., p. 186

from HSDB

4.35

SANGSTER (1993)

from Human Metabolome Database (HMDB); ILO International Chemical Safety Cards (ICSC)

3.2.7 Decomposition

When heated to decomposition it emits toxic fumes of /hydrogen chloride and nitrogen oxides/.

Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 2191

from HSDB

3.2.8 Dissociation Constants

pKa1 = 3.96 (amine); pKa2 = 6.75 (imine) (est)

ChemSpider; Ketoconazole (65277-42-1). London, UK: Royal Chemical Society. Available from, as of Aug 27, 2014: http://www.chemspider.com/Search.aspx

from HSDB

pKa = 4.6 (est)

*SPARC; pKa/property server. Ver 3. Jan, 2006. Available from, as of May3, 2006: **http://ibmlc2.chem.uga.edu/sparc/***

from HSDB

3.2.9 Other Experimental Properties

Henry's Law constant = 5.59X10-20 atm cu m/mole at 25 deg C (est)

*US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.11. Nov, 2012. Available from, as of Aug 27, 2014: **http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm***

from HSDB

Hydroxyl radical reaction rate constant = 2.36X10-10 cu cm/molec-sec at 25 deg C (est)

*US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.11. Nov, 2012. Available from, as of Aug 27, 2014: **http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm***

from HSDB

4 Spectral Information

4.1 1D NMR Spectra

4.1.1 13C NMR Spectra

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Thumbnail	

from SpectraBase

4.2 Mass Spectrometry

MoNA ID	SM857403
MS Category	Experimental
MS Type	Chromatography identified as LC-MS
MS Level	MS2
Precursor Type	[M+H]+
precursor m/z	531.156
Instrument	Q Exactive Plus Orbitrap Thermo Scientific
Instrument Type	LC-ESI-QFT
Ionization	ESI
Ionization Mode	positive
Collision Energy	35 (nominal)
Retention Time	9.348 min
Splash	splash10-001i-3530190000-a2b05a2498270bcd4a7e
Thumbnail	

Submitter	CASMI Team, UFZ, Eawag

from MassBank of North America (MoNA)

4.2.1 GC-MS

GC-MS	GC-MS Spectrum 19970 - HMDB HMDB0012242

from Human Metabolome Database (HMDB)

4.2.2 MS-MS

MS-MS	MS-MS Spectrum 263775 - HMDB HMDB0012242 MS-MS Spectrum 263776 - HMDB HMDB0012242 MS-MS Spectrum 263777 - HMDB HMDB0012242 MS-MS Spectrum 283704 - HMDB HMDB0012242 MS-MS Spectrum 283705 - HMDB HMDB0012242 MS-MS Spectrum 283706 - HMDB HMDB0012242 MS-MS Spectrum 452384 - HMDB HMDB0012242

from Human Metabolome Database (HMDB)

4.3 IR Spectra

4.3.1 ATR-IR Spectra

Instrument Name	Bio-Rad FTS
Technique	ATR-Neat (DuraSamplIR II) ground
Source of Spectrum	Forensic Spectral Research
Source of Sample	Biomol International, L.P.
Catalog Number	EI-107
Lot Number	P1446ap
Copyright	Copyright © 2009-2018 Bio-Rad Laboratories, Inc. All Rights Reserved.
Thumbnail	

from SpectraBase

4.4 Raman Spectra

Technique	FT-Raman
Source of Spectrum	Forensic Spectral Research
Source of Sample	Biomol International, L.P.
Catalog Number	EI-107
Lot Number	P1446ap

Copyright	Copyright © 2012-2018 Bio-Rad Laboratories, Inc. All Rights Reserved.
Thumbnail	

from SpectraBase

5 Related Records

5.1 Related Compounds with Annotation

from PubChem

5.2 Related Compounds

Same Connectivity	15 Records
Same Stereo	3 Records
Same Isotope	9 Records
Same Parent, Connectivity	38 Records
Same Parent, Stereo	5 Records
Same Parent, Isotope	32 Records
Same Parent, Exact	3 Records
Mixtures, Components, and Neutralized Forms	4 Records
Similar Compounds	840 Records
Similar Conformers	84 Records

from PubChem

5.3 Substances

5.3.1 Related Substances

All	78 Records
Same	74 Records
Mixture	4 Records

from PubChem

5.3.2 Substances by Category

from PubChem

5.4 Entrez Crosslinks

PubMed	45 Records
Protein Structures	2 Records

from PubChem

5.5 NCBI LinkOut

from NCBI

6 Chemical Vendors

from PubChem

7 Drug and Medication Information

7.1 Drug Indication

Showing 3 of 4 View More

Ketoconazole HRA is indicated for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years.

▸ from EU Community Register of Medicinal Products

Treatment of granulosa cell tumours

▸ from EU Community Register of Medicinal Products

Treatment of Cushing's syndrome

▸ from EU Community Register of Medicinal Products

7.2 LiverTox Summary

Ketoconazole is an imidazole fungicidal agent with a very broad spectrum of activity against many fungal species that is used for treatment of superficial and systemic fungal infections. Ketoconazole is a well documented cause of clinically apparent acute drug induced liver injury and is no longer recommended as a first line antifungal agent.

▸ from LiverTox

7.3 Drug Classes

Antifungal Agents

▸ from LiverTox

7.4 FDA Medication Guides

Drug	Active Ingredient	Form;Route	Company	Date
Nizoral	Ketoconazole	TABLET;ORAL	JANSSEN PHARMS	02/25/2014

▸ from FDA Medication Guides

7.5 FDA Orange Book

▸ from FDA Orange Book

7.6 Drug Labels for Ingredients

Label Information	Total 134 labels
Drug Ingredient	KETOCONAZOLE
NDC Code(s)	0093-3219-15, 0093-3219-30, 0093-3219-92, 0168-0099-15, 0168-0099-30, 0168-0099-60, 0378-0261-01, 0378-7007-01, 0378-7007-50, 0378-8136-01 ... total 224.
Packagers	A-S Medication Solutions; Aidarex Pharmaceuticals LLC; Animal Pharmaceuticals; Aqua Pharmaceuticals; Bayer HealthCare LLC; Bryant Ranch Prepack; Carilion Materials Management; Ceva Sante Animale; DIRECT RX; Davis Manufacturing and Packaging Inc ... total 56.

▸ from DailyMed

7.7 Clinical Trials

7.7.1 ClinicalTrials.gov

from ClinicalTrials.gov

7.7.2 EU Clinical Trials Register

from EU Clinical Trials Register

7.8 European Medicines Agency (EMA)

Showing 2 of 19 View More

Medicine	Ketoconazole HRA
Category	Human; Orphan
Therapeutic area	Cushing Syndrome
Active Substance	Ketoconazole
INN/Common name	ketoconazole
Pharmacotherapeutic Classes	ANTIMYCOTICS FOR SYSTEMIC USE
Indication/Condition	Ketoconazole HRA is indicated for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years.
Status	This medicine is authorized for use in the European Union
Company	Laboratoire HRA Pharma
Market Date	2014-11-17

from European Medicines Agency (EMA)

Medicine	Ketoconazole HRA
Category	Human, Rare disease (orphan)
Disease/Condition	Treatment of Cushing's syndrome
Active Substance	Ketoconazole
Status of Orphan Designation	Positive
Decision Date	2012-04-23

from European Medicines Agency (EMA)

7.9 Therapeutic Uses

Antifungal agents

National Library of Medicine's Medical Subject Headings. Ketoconazole. Online file (MeSH, 2014). Available from, as of August 28, 2014: ***http://www.nlm.nih.gov/mesh/2014/mesh_browser/MBrowser.html***

from HSDB

Nizoral Tablets should be used only when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks. **Nizoral** (ketoconazole) Tablets are indicated for the treatment of the following systemic fungal infections in patients who have failed or who are intolerant to other therapies: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. **Nizoral** Tablets should not be used for fungal meningitis because it penetrates poorly into the cerebrospinal fluid. /Included in US product label/

NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: ***http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465***

from HSDB

Oral ketoconazole has been used for the palliative treatment of Cushing's syndrome (hypercortisolism), including adrenocortical hyperfunction associated with adrenal or pituitary adenoma or ectopic corticotropin-secreting tumors. Based on ketoconazole's endocrine effects, the drug has been used in the treatment of advanced prostatic carcinoma. Safety and efficacy of ketoconazole have not been established for either of these indications. Oral ketoconazole also has been used in the treatment of hypercalcemia in patients with sarcoidosis and the treatment of tuberculosis-associated hypercalcemia and idiopathic infantile hypercalcemia and hypercalciuria. /NOT included in US product label/

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Ketoconazole has been used for the treatment of sporotrichosis caused by Sporothrix schenckii; however, the drug is not recommended since it is less effective and associated with more adverse effects than some other azoles. Oral **itraconazole** is considered the drug of choice for the treatment of cutaneous, lymphocutaneous, or mild pulmonary or osteoarticular sporotrichosis and for follow-up therapy in more severe infections after a response has been obtained with IV **amphotericin B**. /NOT included in US product label/

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Because of ketoconazole's ability to inhibit testicular and adrenal steroid synthesis, the drug has been used in the treatment of advanced prostatic carcinoma. Ketoconazole has been used as a first-line agent in a few patients, but usually has been used as second-line hormonal therapy in patients with stage IV recurrent prostatic cancer. A limited number of patients with androgen-independent prostatic cancer have received ketoconazole in conjunction with **doxorubicin**. Ketoconazole has been used effectively as an adjunct in the acute management of disseminated intravascular coagulation (DIC) associated with prostatic carcinoma in a limited number of patients. Safety and efficacy of ketoconazole for the treatment of advanced prostate cancer have not been established and the drug is not labeled by the FDA for this use. /NOT included in US product label/

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Oral ketoconazole has been used in conjunction with topical anti-infective agents (e.g., **miconazole**, **neomycin**, **metronidazole**, **propamidine isethionate**) in the treatment of Acanthamoeba keratitis. Optimum therapy for Acanthamoeba keratitis remains to be clearly established, but prolonged local and systemic therapy with multiple anti-infective agents and, often, surgical treatment (e.g., penetrating keratoplasty) are usually required. A regimen of oral ketoconazole, **rifampin**, and **co-trimoxazole** has been used successfully for the treatment of chronic Acanthamoeba meningitis in several immunocompetent children. /NOT included in US product label/

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Ketoconazole has been effective in a few adolescents for the treatment of tuberculosis-associated hypercalcemia. Ketoconazole also has been effective in a few infants for the treatment of idiopathic infantile hypercalcemia and hypercalciuria. /NOT included in US product label/

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Ketoconazole has been used with some success for the treatment of hypercalcemia in adults with sarcoidosis. By competitively inhibiting synthesis of **1,25-dihydroxyvitamin D**, ketoconazole may reduce elevated serum concentrations of the vitamin that apparently may contribute to sarcoidosis-associated hypercalcemia. Ketoconazole has been shown to produce a dose-dependent decrease in serum **1,25-dihydroxyvitamin D** concentrations in healthy individuals and hypercalcemic patients with primary hyperparathyroidism. However, while ketoconazole generally decreases serum concentrations of the vitamin, the drug has reduced serum **calcium** concentrations in some, but not all, patients with sarcoidosis-associated hypercalcemia. In addition, hypercalcemia and increased serum **1,25-dihydroxyvitamin D** concentrations may recur when ketoconazole dosage is decreased or the drug discontinued. Corticosteroids generally are considered first-line treatment of sarcoidosis-associated hypercalcemia; ketoconazole is considered an alternative in patients who fail to respond to or cannot tolerate corticosteroids. /NOT included in US product label/

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Although further study is needed, ketoconazole has been used with some success in a limited number of patients for the treatment of dysfunctional hirsutism and in a limited number of boys for the treatment of precocious puberty. /NOT included in US product label/

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Although oral ketoconazole has been used for the treatment of certain Candida infections (e.g., oropharyngeal and/or esophageal candidiasis, vulvovaginal candidiasis, candiduria, chronic mucocutaneous candidiasis) and the treatment of dermatophyte infections (e.g., tinea capitis, tinea corporis, tinea pedis, tinea unguium [onychomycosis]), the drug is no longer recommended and no longer labeled by the US Food and Drug Administration (FDA) for these uses. /NOT included in US product label/

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

/Ketoconazole/ ... also has been used effectively for the topical treatment of tinea manuum caused by Trichophyton and tinea corporis caused by Microsporum. Like other **imidazole** derivatives (e.g., **clotrimazole**, **econazole**, **miconazole**, **oxiconazole**, **sulconazole**) and **ciclopirox olamine**, ketoconazole has an advantage over some other topical antifungal agents (e.g., **nystatin**, **tolnaftate**) in the treatment of mixed infections or for empiric treatment pending identification of the causative organism since the drug is active against both dermatophytes and Candida. /NOT included in US product label/

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Ketoconazole is used topically as a 2% cream for the treatment of cutaneous candidiasis caused by C. albicans. Like other **imidazole** derivatives (e.g., **clotrimazole**, **econazole**, **miconazole**, **oxiconazole**, **sulconazole**) and **ciclopirox olamine**, ketoconazole has an advantage over some other topical antifungals (e.g., **nystatin**, **tolnaftate**) in the treatment of mixed infections or for empiric treatment pending identification of the causative organism since the drug is active against both dermatophytes and Candida. /Included in US product label/

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Ketoconazole is used topically for the treatment of seborrheic dermatitis, including seborrheic dermatitis of the scalp. Ketoconazole also is used topically for self-medication for the reduction of flaking, scaling, and itching associated with dandruff. /Included in US product label/

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Ketoconazole is used topically as a 2% cream or 2% shampoo for the treatment of pityriasis (tinea) versicolor, a superficial infection caused by or presumed to be caused by Malassezia furfur. /Included in US product label/

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

An extemporaneously prepared ophthalmic suspension containing ketoconazole 2% has been used with some success in a limited number of patients for the topical treatment of fungal keratitis caused by Alternaria, Aspergillus, Fusarium, or Mycelia sterilia. However, in rabbits, ketoconazole has generally been ineffective for the topical treatment of Aspergillus fumigatus keratitis or C. albicans corneal infections. /NOT included in US product label/

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Ketoconazole 2% cream has been used with good results in combination with a topical corticosteroid (**beclomethasone dipropionate** or **clobetasone butyrate**) and an antibacterial agent (**fusidate sodium**) for the treatment of a variety of dermatoses that frequently involve fungal or bacterial superinfections (e.g., atopic dermatitis, diaper rash, eczema, folliculitis, impetigo, intertrigo, lichenoid dermatitis, psoriasis. /NOT included in US product label/

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Ketoconazole is used topically as a 2% cream for the treatment of tinea corporis, tinea cruris, and tinea pedis caused by Epidermophyton floccosum, Trichophyton mentagrophytes, or T. rubrum. ... Like other **imidazole** derivatives (e.g., **clotrimazole**, **econazole**, **miconazole**, **oxiconazole**, **sulconazole**) and **ciclopirox olamine**, ketoconazole has an advantage over some other topical antifungal agents (e.g., **nystatin**, **tolnaftate**) in the treatment of mixed infections or for empiric treatment pending identification of the causative organism since the drug is active against both dermatophytes and Candida. /Included in US product label/

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

MEDICATION (VET) Ketoconazole is a synthetic, broad-spectrum antifungal drug belonging to the **imidazole** family. It is a potent inhibitor of **ergosterol** (a main membrane lipid of fungi) synthesis. Fungal cells are thus unable to maintain the integrity of plasma membranes, which leads to cell wall rupture. Because the therapeutic effect of ketoconazole is delayed,

amphotericin B is often used in combination for cases of serious systemic disease. For dermatophytosis, ketoconazole is active against Trichophyton verrucosum, T equinum, T mentagrophytes, Microsporum canis, and M nanum. It is also active against the yeast Malassezia pachydermatis and Cryptococcus neoformans ... . Coccidioidomycosis responds better to ketoconazole than to amphotericin B in many instances, with a minimal treatment period of 12 mo in animals with disseminated disease. Blastomycosis, histoplasmosis, and cryptococcosis may be treated with a combination of ketoconazole and amphotericin B (the combination is not more effective than the latter alone, but there are fewer nephrotoxic signs). For blastomycosis ... amphotericin B is combined with ketoconazole ... . For histoplasmosis, amphotericin B ... is combined with ketoconazole ... .

Kahn, C.M (ed.).; The Merck Veterinary Manual 10th Edition. Merck & Co. Whitehouse Station NJ. 2010, p. 2194

▸ from HSDB

7.10 Drug Warnings

/BOXED WARNING/ WARNING. Nizoral Tablets should be used only when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks. Hepatotoxicity: Serious hepatotoxicity, including cases with a fatal outcome or requiring liver transplantation has occurred with the use of oral ketoconazole. Some patients had no obvious risk factors for liver disease. Patients receiving this drug should be informed by the physician of the risk and should be closely monitored. QT Prolongation and Drug Interactions Leading to QT Prolongation: Co-administration of the following drugs with ketoconazole is contraindicated: dofetilide, quinidine, pimozide, cisapride, methadone, disopyramide, dronedarone, ranolazine. Ketoconazole can cause elevated plasma concentrations of these drugs and may prolong QT intervals, sometimes resulting in life-threatening ventricular dysrhythmias such as torsades de pointes.

NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465

▸ from HSDB

Transient increases in serum AST, ALT, and alkaline phosphatase concentrations may occur during ketoconazole therapy. Serious hepatotoxicity has occurred in patients receiving oral ketoconazole, including cases that were fatal or required liver transplantation. Hepatotoxicity may be hepatocellular (in most cases), cholestatic, or a mixed pattern of injury. Although ketoconazole-induced hepatotoxicity usually is reversible following discontinuance of the drug, recovery may take several months and rarely death has occurred. Symptomatic hepatotoxicity usually is apparent within the first few months of ketoconazole therapy, but occasionally may be apparent within the first week of therapy. Some patients with ketoconazole-induced hepatotoxicity had no obvious risk factors for liver disease. Serious hepatotoxicity has been reported in patients receiving high oral ketoconazole dosage for short treatment durations and in patients receiving low oral dosage of the drug for long durations. Many of the reported cases of hepatotoxicity occurred in patients who received the drug for the treatment of tinea unguium (onychomycosi or the treatment of chronic, refractory dermatophytoses. Ketoconazole-induced hepatitis has been reported in some children.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014, p. 521

▸ from HSDB

Coadministration of a number of CYP3A4 substrates such as dofetilide, quinidine cisapride and pimozide is contraindicated with Nizoral Tablets. Coadministration with ketoconazole can cause elevated plasma concentrations of these drugs and may increase or prolong both therapeutic and adverse effects to such an extent that a potentially serious adverse reaction may occur. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and sometimes resulting in life-threatening ventricular tachyarrhythmias including occurrences of torsades de pointes, a potentially fatal arrhythmia. Additionally, the following other drugs are contraindicated with Nizoral Tablets: methadone, disopyramide, dronedarone, ergot alkaloids such as dihydroergotamine, ergometrine, ergotamine, methylergometrine, irinotecan, lurasidone, oral midazolam, alprazolam, triazolam, felodipine, nisoldipine, ranolazine, tolvaptan, eplerenone, lovastatin, simvastatin and colchicine.

NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465

▸ from HSDB

The use of Nizoral Tablets is contraindicated in patients with acute or chronic liver disease.

NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465

▸ from HSDB

Concomitant administration of ergot alkaloids such as dihydroergotamine and ergotamine with Nizoral Tablets is contraindicated.

NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465

▸ from HSDB

Coadministration of CYP3A4 metabolized HMG-CoA reductase inhibitors such as simvastatin, and lovastatin is contraindicated with Nizoral Tablets.

NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465

▸ from HSDB

Coadministration of Nizoral Tablets with oral midazolam, oral triazolam or alprazolam has resulted in elevated plasma concentrations of these drugs. This may potentiate and prolong hypnotic and sedative effects, especially with repeated dosing or chronic administration of these agents. Concomitant administration of Nizoral Tablets with oral triazolam, oral midazolam or alprazolam is contraindicated.

NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465

from HSDB

Ketoconazole can prolong the QT interval. Data from clinical studies and drug interaction studies indicate that an oral ketoconazole dosage of 200 mg twice daily for 3-7 days can increase the corrected QT (QTc) interval; a mean maximum increase of about 6-12 msec has been reported approximately 1-4 hours after a dose. Hypertension has been reported in some patients receiving high-dose ketoconazole therapy (e.g., 400 mg every 6-8 hours) for metastatic prostatic carcinoma. Although not clearly established, it has been suggested that ketoconazole-induced increases in mineralocorticoid activity may have caused the increase in blood pressure observed in these patients. Peripheral edema and orthostatic hypotension also have been reported.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Headache, dizziness, somnolence, asthenia, fatigue, malaise, nervousness, insomnia, and paresthesia have been reported in patients receiving ketoconazole. Reversible increased intracranial pressure (e.g., papilledema, bulging fontanelles in infants) has occurred in patients receiving ketoconazole.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Vomiting, nausea, diarrhea, constipation, abdominal or upper abdominal pain, anorexia, increased appetite, dry mouth, dysgeusia, dyspepsia, flatulence, and tongue discoloration have been reported in patients receiving ketoconazole.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Ketoconazole dosages of 400 mg or higher decrease adrenal corticosteroid secretion. The drug can inhibit cortisol synthesis, particularly in patients receiving relatively high daily dosages or divided daily dosing of the drug. The adrenocortical response to corticotropin (ACTH) may be at least transiently diminished and a reduction in urinary free and serum cortisol concentrations can occur during therapy with the drug; adrenocortical insufficiency has been reported rarely.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Anaphylaxis has been reported after the first dose of ketoconazole. Other hypersensitivity reactions, including anaphylactoid reaction, erythema multiforme, rash, dermatitis, erythema, urticaria, and pruritus, have been reported in patients receiving ketoconazole. Acute generalized exanthematous pustulosis, photosensitivity, angioneurotic edema, alopecia, and xeroderma also have been reported.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Gynecomastia has been reported in patients receiving ketoconazole. Bilateral gynecomastia with breast tenderness has occurred in some men during ketoconazole therapy. In some patients, gynecomastia and breast pain abated after several weeks of continued treatment with the drug. In other patients, gynecomastia persisted until ketoconazole was discontinued. Limited data suggest that gynecomastia occurs because ketoconazole decreases serum testosterone concentrations and to a lesser extent serum estradiol concentrations, resulting in an increased estradiol: testosterone ratio. Although it has been suggested that gynecomastia may be caused by a direct effect on breast tissue since serum hormone concentrations were normal in several patients, ketoconazole only transiently inhibits testosterone synthesis and testosterone concentrations may have returned to baseline values depending on when the serum samples were obtained.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Arthralgia, myalgia, fever, chills, hot flush, photophobia, epistaxis, menstrual disorder, impotence, and thrombocytopenia have been reported in patients receiving ketoconazole. Alcohol intolerance has been reported in patients receiving ketoconazole.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Nizoral Tablets have not been systematically studied in children of any age, and essentially no information is available on children under 2 years. Nizoral Tablets should not be used in pediatric patients unless the potential benefit outweighs the risks.

NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465

from HSDB

There are no adequate and well controlled studies in pregnant women. **Nizoral** Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: **http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465***

▸ **from HSDB**

Adverse effects have been reported in up to 5% of patients receiving topical ketoconazole 2% cream and have consisted principally of local reactions such as severe irritation, pruritus, and stinging. A painful allergic reaction, consisting of localized swelling and inflammation, occurred in at least one patient receiving ketoconazole 2% cream.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ **from HSDB**

FDA Pregnancy Risk Category: C /RISK CANNOT BE RULED OUT. Adequate, well controlled human studies are lacking, and animal studies have shown risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is given during pregnancy; but the potential benefits may outweigh the potential risk./

*NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: **http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465***

▸ **from HSDB**

Ketoconazole has been shown to be excreted in the milk. Mothers who are under treatment with **Nizoral** Tablets should not breast feed.

*NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: **http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465***

▸ **from HSDB**

Although hepatotoxicity, decreased **testosterone** concentrations, and decreased corticotropin (ACTH)-induced corticosteroid concentrations have been reported with oral ketoconazole, these adverse effects have not been reported with topical ketoconazole and are unlikely since the drug does not appear to be appreciably absorbed following topical application to skin.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ **from HSDB**

Following topical application of ketoconazole 2% shampoo to the skin, adverse effects include pruritus, application site reaction, and dry skin. Adverse effects reported following topical application of ketoconazole 2% shampoo to the scalp include increased hair loss, irritation, abnormal hair texture, scalp pustules, dry skin, pruritus, and oiliness or dryness of the hair and scalp. In some patients with permanently waved ("permed") hair, use of ketoconazole 2% shampoo resulted in loss of the curl.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ **from HSDB**

The most frequently reported adverse effects in patients using topical ketoconazole 2% gel are burning at the application site and headache. In studies evaluating the potential of topical ketoconazole 2% gel for causing dermal irritation, contact sensitization, or phototoxic or photoallergenic reactions, the gel caused irritation, but did not cause contact sensitization, phototoxicity, or photoallergenicity.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ **from HSDB**

The most frequently reported adverse effects in patients using topical ketoconazole 2% foam include burning and application site reactions. Application site reactions reported in up to 1% of patients include dryness, erythema, irritation, paresthesia, pruritus, rash, and warmth.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ **from HSDB**

Some formulations of ketoconazole 2% cream contain **sodium sulfite**, which may cause allergic-type reactions (including anaphylaxis and life-threatening or less severe asthmatic episodes) in certain susceptible individuals. he overall prevalence of **sulfite** sensitivity in the general population is unknown, but probably low; such sensitivity appears to occur more frequently in asthmatic than in nonasthmatic individuals.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ **from HSDB**

Contact dermatitis has been reported following topical application of other **imidazole**-derivative **azole** antifungals (e.g., **clotrimazole**, **econazole**, **miconazole**, **oxiconazole**, **sulconazole**, **tioconazole**). Cross-sensitization appears to occur among the **imidazole** derivatives; however, cross-sensitivity appears to be unpredictable. The fact that patients with contact sensitivity to one **imidazole**-derivative **azole** antifungal may be sensitive to other similar drugs should be considered.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ **from HSDB**

Rarely, ketoconazole 2% cream or one of its excipients (e.g., **sodium sulfite**, prophylene glycol) has been associated with contact dermatitis. Topical application of ketoconazole 2% foam may cause contact sensitization or photoallergenicity.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Since it is not known whether ketoconazole is distributed into milk following topical application, the manufacturers of ketoconazole 2% cream recommend that a decision be made to discontinue nursing or the cream. The manufacturers of ketoconazole 2% foam and gel state the drugs should be used with caution in nursing women. Although ketoconazole 2% shampoo is not detected in plasma following chronic application, the shampoo should be used with caution in nursing women. Nursing women considering self-medication with the 1% shampoo should consult a clinician before using the preparation.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Ketoconazole 2% cream, foam, gel, or shampoo should be used during pregnancy only when the potential benefits justify the possible risks to the fetus. Pregnant women considering self-medication with ketoconazole 1% shampoo should consult a clinician before using the preparation.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Safety and efficacy of ketoconazole 2% cream have not been established in children. Topical ketoconazole 2% cream has been used without unusual adverse effect in a limited number of children 2 days to 12 years of age. Safety and efficacy of ketoconazole 2% foam or gel have not been established in children younger than 12 years of age. Safety and efficacy of ketoconazole 2% shampoo have not been established in children. Safety and efficacy of ketoconazole 1% shampoo for self-medication have not been established in children younger than 12 years of age.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Patients receiving ketoconazole 1% shampoo for self-medication of dandruff should be advised to not use the shampoo if the scalp is broken or inflamed and to avoid contact with the eyes. They also should be advised to discontinue the shampoo and contact a clinician if rash occurs or the condition worsens or does not improve within 2-4 weeks since these may be signs of a serious condition.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Commercially available ketoconazole 2% cream, foam, or gel is intended for topical application to the skin only and should not be applied to the eyes and should not be administered intravaginally. The 1 and 2% shampoos also are intended for topical application only and should not be applied to the eyes; if contact with the eyes occurs, the eyes should be rinsed thoroughly with **water**.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Topically applied ketoconazole appears to have a low order of toxicity and is generally well tolerated.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Ketoconazole is contraindicated in women of childbearing potential unless effective forms of contraception are employed.

*Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p2 (Revision date: March 4, 2014). Available from, as of November 12, 2014: **http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

Since ketoconazole influences steroid synthesis, the potential for a deleterious effect on puberty and/or fertility must be carefully considered when long-term therapy is contemplated in children. Anaphylactic reactions to ketoconazole with severe angioedema have been reported.

*Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p6 (Revision date: March 4, 2014). Available from, as of November 12, 2014: **http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

If clinical signs or symptoms develop that are consistent with liver disease, such as anorexia, nausea, vomiting, jaundice, fatigue, abdominal pain, dark urine, or pale stools, treatment should be discontinued and liver function testing performed.

*Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p4 (Revision date: March 4, 2014). Available from, as of November 12, 2014: **http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

Transient minor elevations in liver enzymes have occurred during treatment with ketoconazole tablets. The drug should be discontinued if liver enzyme abnormalities persist, if the enzyme abnormalities worsen, or if the abnormalities are associated with symptoms of hepatotoxicity.

*Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p4 (Revision date: March 4, 2014). Available from, as of November 12, 2014: **http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

Liver function must be monitored in all patients who are receiving ketoconazole tablets. Tests should be done before starting treatment, at week 2 and week 4 of treatment, and then continued monthly. Treatment should be stopped if any liver parameters are elevated above 3 times the normal limit.

*Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p4 (Revision date: March 4, 2014). Available from, as of November 12, 2014: **http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

VET In dogs, the most common adverse effects are inappetence, vomiting, pruritus, alopecia, and reversible lightening of the hair coat. Anorexia may be reduced by administering the dose with food. Cats appear to be more sensitive to ketoconazole. Clinical signs of toxicity include anorexia, fever, depression, diarrhea, and increased liver enzymes. ... Hepatotoxicity (cholangiohepatitis and increased liver enzymes) has also been reported.

Kahn, C.M (ed.).; The Merck Veterinary Manual 10th Edition. Merck & Co. Whitehouse Station NJ. 2010, p. 2194-5

▸ from HSDB

VET Although ketoconazole has been used extensively in dogs for the treatment of various fungal infections, information about adverse effects is mainly anecdotal. Common adverse effects in humans include dose-dependant anorexia, nausea and vomiting, allergic rashes and pruritus. Drug-induced hepatitis is very rare, but potentially fatal. The aim of this study was to evaluate the type and frequency of adverse effects associated with ketoconazole therapy in dogs treated for skin diseases and any possible influence of dosage, duration of therapy, signalment or concurrent medication. The medical records of 632 dogs treated with ketoconazole (2.6-33.4 mg/kg) were reviewed. Adverse effects occurred in 14.6% (92 dogs) and included vomiting (7.1%), anorexia (4.9%), lethargy (1.9%), diarrhea (1.1%), pruritus (0.6%), erythema (0.3%) and other adverse effects (2.5%). Of the dogs with other adverse effects, four of 16 (25%) were ataxic and three of these received concurrent **ivermectin**. Adverse effects were significantly more often recorded in dogs concurrently treated with **ciclosporin** (P = 0.034) or **ivermectin** (P = 0.007). Increased liver enzyme levels were reported rarely, and icterus was not seen in any of the dogs. However, monitoring liver enzymes during therapy is recommended, although this might not necessarily prevent severe idiosyncratic hepatotoxicity. **PubMed Abstract**

Mayer UK et al; Vet Dermatol 19 (4): 199-208 (2008)

▸ from HSDB

Concomitant use of **mefloquine** (single 500-mg dose) and ketoconazole (400 mg once daily for 10 days) in healthy adults increased the mean peak plasma concentration and AUC of **mefloquine** by 64 and 79%, respectively, and increased the mean elimination half-life of **mefloquine** from 322 hours to 448 hours. Because of the risk of a potentially fatal prolongation of the corrected QT (QTc) interval, the manufacturer of **mefloquine** states that ketoconazole should not be used concomitantly with **mefloquine** or within 15 weeks after the last **mefloquine** dose.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of **pimozide** and ketoconazole is contraindicated. Concomitant use of the drugs may increase **pimozide** plasma concentrations and lead to QTc interval prolongation, sometimes resulting in serious life-threatening ventricular tachyarrhythmias such as torsades de pointes.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of **dofetilide** and ketoconazole is contraindicated. Concomitant use of the drugs may increase **dofetilide** plasma concentrations and lead to QTc interval prolongation, sometimes resulting in serious life-threatening ventricular tachyarrhythmias such as torsades de pointes.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of **quinidine** and ketoconazole is contraindicated. Concomitant use of the drugs may increase **quinidine** plasma concentrations and lead to QTc interval prolongation, sometimes resulting in serious life-threatening ventricular tachyarrhythmias such as torsades de pointes.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of ketoconazole and **cisapride** (available in the US only under a limited-use protocol) is contraindicated. Ketoconazole potentially inhibits metabolism of **cisapride**. Concomitant use of ketoconazole and **cisapride** has resulted in increased **cisapride** plasma concentrations and AUC; QT interval prolongation and serious cardiovascular effects, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes, have been reported rarely.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Concomitant use of ketoconazole and drugs that are CYP3A4 substrates that prolong the QT interval (e.g., **cisapride**, **dofetilide**, **pimozide**, **quinidine**) may increase plasma concentrations of the concomitantly administered CYP3A4 substrate, which can lead to QT interval prolongation, sometimes resulting in life-threatening ventricular dysarrhythmias such as torsades de pointes. Concomitant use of ketoconazole and these drugs that prolong the QT interval is contraindicated.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Concomitant use of ketoconazole and **atorvastatin** or **lovastatin** is contraindicated. Concomitant use of **hydroxymethylglutaryl-CoA** (**HMG-CoA**) reductase inhibitors (statins) metabolized by CYP3A (e.g., **atorvastatin**, **lovastatin**) and ketoconazole may increase plasma concentrations of the statin resulting in increased effects and increased risk of statin-associated adverse effects, including myopathy and rhabdomyolysis.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

7.11 Drug Tolerance

Strains of Candida albicans resistant to ketoconazole have been isolated from patients who received the drug. C. albicans resistant to ketoconazole may also be cross-resistant to other **azole** antifungal agents (eg, **fluconazole**, **itraconazole**).

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

8 Pharmacology and Biochemistry

8.1 Pharmacology

Ketoconazole is a synthetic derivative of **phenylpiperazine** with broad antifungal properties and potential antineoplastic activity. Ketoconazole inhibits sterol 14-a-dimethylase, a microsomal cytochrome P450-dependent enzyme, thereby disrupting synthesis of **ergosterol**, an important component of the fungal cell wall. (NCI04)

from NCIt

8.2 MeSH Pharmacological Classification

Cytochrome P-450 CYP3A Inhibitors

Drugs and compounds which inhibit or antagonize the biosynthesis or actions of CYTOCHROME P-450 CYP3A. (See **all compounds classified as Cytochrome P-450 CYP3A Inhibitors**.)

from MeSH

Antifungal Agents

Substances that destroy fungi by suppressing their ability to grow or reproduce. They differ from FUNGICIDES, INDUSTRIAL because they defend against fungi present in human or animal tissues. (See **all compounds classified as Antifungal Agents**.)

from MeSH

14-alpha Demethylase Inhibitors

Compounds that specifically inhibit STEROL 14-DEMETHYLASE. A variety of azole-derived ANTIFUNGAL AGENTS act through this mechanism. (See **all compounds classified as 14-alpha Demethylase Inhibitors**.)

from MeSH

8.3 ATC Code

Anatomical main group: J - General antiinfectives for systemic use

Therapeutic subgroup: J02 - Antimycotics for systemic use

Pharmacological subgroup: J02A - Antimycotics for systemic use

Chemical subgroup: J02AB - **Imidazole** derivatives

Chemical substance: J02AB02 - ketoconazole

from EU Community Register of Medicinal Products

J02AB02

from European Medicines Agency (EMA)

D - Dermatologicals

D01 - Antifungals for dermatological use

D01A - Antifungals for topical use

D01AC - Imidazole and triazole derivatives

D01AC08 - Ketoconazole

from WHO ATC

G - Genito urinary system and sex hormones

G01 - Gynecological antiinfectives and antiseptics

G01A - Antiinfectives and antiseptics, excl. combinations with corticosteroids

G01AF - Imidazole derivatives

G01AF11 - Ketoconazole

from WHO ATC

J - Antiinfectives for systemic use

J02 - Antimycotics for systemic use

J02A - Antimycotics for systemic use

J02AB - Imidazole derivatives

J02AB02 - Ketoconazole

from WHO ATC

8.4 Absorption, Distribution and Excretion

Ketoconazole is rapidly absorbed from the GI tract. Following oral administration, ketoconazole is dissolved in gastric secretions and converted to the hydrochloride salt prior to absorption from the stomach.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

The effect of food on the rate and extent of GI absorption of ketoconazole has not been clearly determined. Some clinicians have reported that administration of ketoconazole to fasting individuals results in higher plasma concentrations of the drug than does administration with food. However, the manufacturer states that administration of ketoconazole with food increases the extent of absorption and results in more consistent plasma concentrations of the drug. The manufacturer suggests that food increases absorption of ketoconazole by increasing the rate and/or extent of dissolution of ketoconazole (e.g., by increasing bile secretions) or by delaying stomach emptying.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Ketoconazole is a weak dibasic agent and thus requires acidity for dissolution and absorption.

*NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: **http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465***

from HSDB

The bioavailability of oral ketoconazole depends on the pH of the gastric contents in the stomach; an increase in the pH results in decreased absorption of the drug. Decreased bioavailability of ketoconazole has been reported in patients with acquired immunodeficiency syndrome (AIDS), probably because of gastric hypochlorhydria associated with this condition; concomitant administration of dilute **hydrochloric acid** solution normalized absorption of the drug in these patients.198 Concomitant administration of an acidic beverage may increase bioavailability of oral ketoconazole in some individuals with achlorhydria.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Limited pharmacokinetic data are available on the use of NIizoral Tablets in the pediatric population. Measurable ketoconazole plasma concentrations have been observed in pre-term infants (single or daily doses of 3 to 10 mg/kg) and in pediatric patients 5 months of age and older (daily doses of 3 to 13 mg/kg) when the drug was administered as a suspension, tablet or crushed tablet. Limited data suggest that absorption may be greater when the drug is administered as a suspension compared to a crushed tablet. Conditions that raise gastric pH may lower or prevent absorption. Maximum plasma concentrations occurred 1 to 2 hours after dosing and were in the same general range as those seen in adults who received a 200-400 mg dose.

*NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: **http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465***

from HSDB

In healthy, fasting adults, peak plasma ketoconazole concentrations of approximately 4.2, 5, or 6.2 mcg/mL occurred 1-2 hours following oral administration of a single 200-mg dose as tablets, a suspension, or a solution, respectively. Following

oral administration of a single 200-mg dose of ketoconazole as tablets to nonfasting adults in another study, peak plasma concentrations of the drug were attained within 1-4 hours and ranged from 1.5-4.5 ug/mL; plasma concentrations of the drug were usually less than 0.05 ug/mL after 24 hours. In one study in adults, a single 200-mg dose of ketoconazole as tablets given with a meal resulted in average plasma concentrations of the drug of 3.2 ug/mL at 1 hour, 2.4 ug/mL at 2 hours, 1.2 mcg/mL at 4 hours, and 0.6 ug/mL at 6 hours. In one study in a limited number of children 4-12 years of age, a single 100-mg oral dose of ketoconazole as tablets resulted in plasma concentrations of the drug ranging from 0.6-2.5 ug/mL 2 hours after the dose. Oral bioavailability of the drug was increased substantially when ketoconazole was administered to children as a suspension rather than as crushed tablets mixed with applesauce; peak plasma concentrations also were higher and occurred sooner with the suspension. Considerable interindividual variations in peak plasma concentrations attained and areas under the concentration-time curves (AUCs) have been reported with a specific oral dose of ketoconazole. In one cross-over study in adults who received single oral doses of ketoconazole of 100 mg, 200 mg, and 400 mg, a comparison of dose versus AUC suggested that ketoconazole undergoes saturable first pass elimination since bioavailability of the lower dose was relatively poor.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

In vitro, the plasma protein binding is about 99% mainly to the albumin fraction. Ketoconazole is widely distributed into tissues; however, only a negligible proportion reaches the cerebrospinal fluid.

NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: ***http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465***

▸ from HSDB

CNS penetration of the drug is unpredictable and has generally been considered to be minimal. In 2 adults with meningitis caused by Coccidioides immitis, a single 400-mg oral dose of ketoconazole resulted in CSF concentrations of the drug of 0.14 ug/mL and 0.21 ug/mL 4 hours after the dose; serum concentrations of ketoconazole in these patients were 2-4 ug/mL 1-2 hours after the dose. In one study in adults with inflamed meninges, CSF concentrations of ketoconazole ranged from 0-0.24 ug/mL at 1-2 hours after a single 200-mg oral dose of the drug and 0-0.85 ug/mL at 1-3.5 hours after a single 400-mg oral dose of the drug. In several other adults with coccidioidal CNS infections, lumbar CSF concentrations of ketoconazole averaged 0.25 ug/mL at 8 hours after an 800-mg oral dose and ranged from 0.27-1.65 ug/mL at 4 hours after a 1.2-g oral dose; ventricular CSF concentrations averaged 50-60% of those attained in lumbar CSF.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Ketoconazole has been shown to be excreted in the milk.

NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: ***http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465***

▸ from HSDB

It is not known if ketoconazole crosses the placenta in humans; however, the drug crosses the placenta in rats.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

In rats, highest concentrations of ketoconazole are attained in the liver, pituitary, and adrenals; moderate concentrations are attained in the lungs, kidneys, bladder, bone marrow, teeth, myocardium, and various glandular tissues; and lowest concentrations are attained in the brain and testes following a single oral dose of the drug.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Approximately 13% of the dose is excreted in the urine, of which 2 to 4% is unchanged drug. The major route of excretion is through the bile into the intestinal tract with about 57% being excreted in the feces.

NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: ***http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465***

▸ from HSDB

In a study in patients with severe seborrheic dermatitis (1-14% of body surface area), topical application of ketoconazole 2% gel once daily for 2 weeks (daily dose 0.05-3.47 g), the mean peak plasma concentration was 1.35 ng/mL on day 7 and 0.8 ng/mL on day 14.1

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

In a study in patients with moderate to severe seborrheic dermatitis, topical application of ketoconazole 2% foam (3 g of ketoconazole) twice daily for 4 weeks resulted in plasma ketoconazole concentrations that were less than 6 ng/mL in 75% of patients; the maximum plasma concentration reported was 11 ng/mL.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

In one study in healthy adults with intact skin, ketoconazole was not detected (lower limits of detection 5 ng/mL) in blood during the 72-hour period immediately following a single topical application to the chest, back, and arms of 10 g of

ketoconazole 2% cream (200 mg of ketoconazole). Following topical application of 80 mg of ketoconazole 2% cream to intact or abraded skin of beagles once daily for 28 days, ketoconazole was not detected in plasma (lower limits of detection 2 ng/mL). In an in vitro model using human skin, ketoconazole was retained in the stratum corneum and boundary of the stratum corneum and stratum granulosum for up to 16 hours following topical application of radiolabeled ketoconazole cream; little or no drug appeared to penetrate into deeper layers of the epidermis.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Ketoconazole does not appear to be appreciably absorbed systemically following topical application to skin or scalp.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Ketoconazole was not detected in plasma of patients who shampooed with ketoconazole 2% shampoo 4-10 times weekly for 6 months or 2-3 times weekly for an average of 16 months (range: 3-26 months).72 Following topical application of ketoconazole 2% shampoo (50 mg/kg) daily for 28 days to intact or abraded skin of rabbits (drug remained on skin for 1 hour before being washed away), ketoconazole was not detected in plasma (lower limits of detection 5 ng/mL). Following a single topical application of ketoconazole 2% shampoo, substantial amounts of the drug were detected on hair 12 hours after application; however only 5% of the applied ketoconazole was detected in hair keratin.103 Following repeated (twice weekly for 2 months) application of ketoconazole 2% shampoo, 20% of the applied dose was detected in hair keratin.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Infant exposure to ketoconazole in human milk was calculated to be 0.4% on average (maximum 1.4%) of those expected from therapeutic doses given directly to infants. ... **PubMed Abstract**

Moretti ME et al; Am J Obstet Gynecol 173 (5): 1625-6

▸ from HSDB

The distribution of a single oral dose of 20 mg/kg 3(H)-ketoconazole was studied in male and female rats. Peak tissue levels of radioactivity were reached one hour after dosing in almost all tissues of the male. Peak times varied somewhat more in females. Tissues were cleared of radioactivity with a half-life similar to that observed in plasma for both males and females, meaning that elimination from tissues was initially faster in males than in females.

*Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p20 (Revision date: March 4, 2014). Available from, as of November 12, 2014: **http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

8.5 Metabolism/Metabolites

Ketoconazole is partially metabolized, in the liver, to several inactive metabolites by oxidation and degradation of the **imidazole** and **piperazine** rings, by oxidative O-dealkylation, and by aromatic hydroxylation.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

8.6 Biological Half-Life

Plasma concentrations of ketoconazole appear to decline in a biphasic manner with a half-life of approximately 2 hours in the initial phase and approximately 8 hours in the terminal phase.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Elimination from plasma is biphasic with a half-life of 2 hours during the first 10 hours and 8 hours thereafter.

*NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: **http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465***

▸ from HSDB

8.7 Mechanism of Action

Ketoconazole blocks the synthesis of **ergosterol**, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme **lanosterol** 14alpha-demethylase responsible for the conversion of **lanosterol** to **ergosterol** in the fungal cell membrane. This results in an accumulation of methylated sterol precursors and a depletion of **ergosterol** within the cell membrane thus weakening the structure and function of the fungal cell membrane.

*NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: **http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465***

▸ from HSDB

Like other azole antifungal agents, ketoconazole presumably exerts its antifungal activity by altering cellular membranes, resulting in increased membrane permeability, secondary metabolic effects, and growth inhibition. Although the exact mechanism of action of ketoconazole has not been fully determined, it has been suggested that the fungistatic activity of the drug may result from interference with ergosterol synthesis, probably via inhibition of C-14 demethylation of sterol intermediates (e.g., lanosterol). The fungicidal activity of ketoconazole at high concentrations may result from a direct physiochemical effect of the drug on the fungal cell membrane.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

8.8 Human Metabolite Information

8.8.1 Metabolite Description

Description

Ketoconazole is only found in individuals that have used or taken this drug. It is a broad spectrum antifungal agent used for long periods at high doses, especially in immunosuppressed patients. [PubChem]Ketoconazole interacts with 14-& alpha; demethylase, a cytochrome P-450 enzyme necessary for the conversion of lanosterol to ergosterol. This results in inhibition of ergosterol synthesis and increased fungal cellular permeability. Other mechanisms may involve the inhibition of endogenous respiration, interaction with membrane phospholipids, inhibition of yeast transformation to mycelial forms, inhibition of purine uptake, and impairment of triglyceride and/or phospholipid biosynthesis. Ketoconazole can also inhibit the synthesis of thromboxane and sterols such as aldosterone, cortisol, and testosterone.

▸ from Human Metabolome Database (HMDB)

8.8.2 Cellular Locations

Cytoplasm Membrane

▸ from Human Metabolome Database (HMDB)

9 Use and Manufacturing

9.1 Overview

Ketoconazole is used as a medication or supplement. An overview is available from MedlinePlus, a consumer health web site produced by the National Library of Medicine.

FOR MORE INFORMATION: (1) National Library of Medicine. MedlinePlus. Available from, as of Aug 30, 2018:
http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682816.html

▸ from HSDB

9.2 Use Classification

EU Pharmaceutical Product Classes	Human drug

▸ from EU Community Register of Medicinal Products

EU Pharmaceutical Product Classes	Human drug

▸ from EU Community Register of Medicinal Products

EU Pharmaceutical Product Classes	Human drug

▸ from EU Community Register of Medicinal Products

EU Pharmaceutical Product Classes	Human drug

▸ from EU Community Register of Medicinal Products

EU Pharmaceutical Product Classes	Human drug

▸ from EU Community Register of Medicinal Products

EMA Classes	Human; Orphan
EMA Pharmacotherapeutic Group	ANTIMYCOTICS FOR SYSTEMIC USE

▸ from European Medicines Agency (EMA)

EMA Classes	Human, Rare disease (orphan)

from European Medicines Agency (EMA)

EMA Classes	Human, Rare disease (orphan)

from European Medicines Agency (EMA)

EMA Classes	Human, Rare disease (orphan)

from European Medicines Agency (EMA)

EMA Classes	Human, Rare disease (orphan)

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EMA Classes	Human, Rare disease (orphan)

from European Medicines Agency (EMA)

EMA Classes	Human, Rare disease (orphan)

from European Medicines Agency (EMA)

9.3 Uses

Antifungal agents

National Library of Medicine's Medical Subject Headings. Ketoconazole. Online file (MeSH, 2014). Available from, as of August 28, 2014: ***http://www.nlm.nih.gov/mesh/2014/mesh_browser/MBrowser.html***

from HSDB

MEDICATION

from HSDB

THERAPEUTIC CATEGORY (VETERINARY): Antifungal

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Cambridge, UK: Royal Society of Chemistry, 2013., p. 983

from HSDB

9.4 Methods of Manufacturing

Preparation: J. Heeres et al., German patent 2804096, eidem, United States of America patents 4144346 and 4223036 (1978, 1979, 1980, all to Janssen).

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Cambridge, UK: Royal Society of Chemistry, 2013., p. 983

from HSDB

9.5 Formulations/Preparations

Tablets as 0.2 g; 2% solutions, ointments, and cream preparations.

Ullmann's Encyclopedia of Industrial Chemistry. 6th ed.Vol 1: Federal Republic of Germany: Wiley-VCH Verlag GmbH & Co. 2003 to Present, p. V. 3 586 (2003)

from HSDB

Trade Names: Candoral, Cetonax, Fitonal, **Fungarest**, Fungicil, Fungo-Hubber, **Fungoral**, Ketazol, **Ketoderm**, Ketoisdin, Ketonan, Ketoral, Micoral, Micotek, Micoticum, **Nizoral**, Nizshampoo, Oromycosal, Oronazol, Panfungol, Rofenid, Terzolin.

Ullmann's Encyclopedia of Industrial Chemistry. 6th ed.Vol 1: Federal Republic of Germany: Wiley-VCH Verlag GmbH & Co. 2003 to Present, p. V. 3 586 (2003)

from HSDB

[See Table #8705 - Ketoconazole Topical Preparations]

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Table #8705 - Ketoconazole Topical Preparations

Route of Administration	Dosage Form	Strength	Brand or Generic Name (Manufacturer)
Topical	Cream	2%	Ketoconazole Cream (Available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name)
Topical	Foam	2%	Extina (Stiefel Laboratories)
Topical	Gel	2%	Xolegel (Barrier Therapeutics)
Topical	Shampoo	1%	Nizoral A-D (McNeil)
Topical	Shampoo	2%	Ketocanazole Shampoo (Available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name)
Topical	Shampoo	2%	Nizoral (Ortho-McNeil)

from HSDB

[See Table #8706 - Ketoconazole Oral Preparations]

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Table #8706 - Ketoconazole Oral Preparations

Route of Administration	Dosage Form	Strength	Brand or Generic Name (Manufacturer)
Oral	Tablets	200 mg	Nizoral (Janssen)
Oral	Tablets	200 mg	Ketoconazole Tablets (Available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name)

from HSDB

9.6 Manufacturers

DailyMed lists 75 formulators for ketoconazole

US Natl Inst Health; DailyMed. Current Medical Information. Available from, as of Aug 25, 2014: ***http://dailymed.nlm.nih.gov/dailymed/about.cfm***

from HSDB

10 Identification

10.1 Analytic Laboratory Methods

Analyte: ketoconazole; matrix: chemical identification; procedure: infrared absorption spectrophotometry with comparison to standards

U.S. Pharmacopeia. The United States Pharmacopeia, USP 29/The National Formulary, NF 24; Rockville, MD: U.S. Pharmacopeial Convention, Inc., p1216 (2006)

from HSDB

Analyte: ketoconazole; matrix: chemical purity; procedure: dissolution in glacial **acetic acid**; potentiometric titration with **perchloric acid**

U.S. Pharmacopeia. The United States Pharmacopeia, USP 29/The National Formulary, NF 24; Rockville, MD: U.S. Pharmacopeial Convention, Inc., p1216 (2006)

from HSDB

Analyte: ketoconazole; matrix: pharmaceutical preparation (oral suspension); procedure: liquid chromatography with detection at 223 nm and comparison to standards (chemical purity)

U.S. Pharmacopeia. The United States Pharmacopeia, USP 29/The National Formulary, NF 24; Rockville, MD: U.S. Pharmacopeial Convention, Inc., p1216 (2006)

from HSDB

Analyte: ketoconazole; matrix: pharmaceutical preparation (tablet); procedure: thin-layer chromatography with comparison to standards (chemical identification)

U.S. Pharmacopeia. The United States Pharmacopeia, USP 29/The National Formulary, NF 24; Rockville, MD: U.S. Pharmacopeial Convention, Inc., p1217 (2006)

from HSDB

Analyte: ketoconazole; matrix: pharmaceutical preparation (tablet); procedure: liquid chromatography with detection at 225 nm and comparison to standards (chemical purity)

U.S. Pharmacopeia. The United States Pharmacopeia, USP 29/The National Formulary, NF 24; Rockville, MD: U.S. Pharmacopeial Convention, Inc., p1217 (2006)

from HSDB

Analyte: ketoconazole; matrix: pharmaceutical preparation (tablet, cream); procedure: high-performance liquid chromatography with ultraviolet detection at 230 nm

Di Pietra AM et al; J Pharm Biomed Anal 10: 873-879 (1992). As cited in: Lunn G, Schmuff N; HPLC Methods for Pharmaceutical Analysis. New York, NY: John Wiley & Sons, 1997., p.795

from HSDB

Analyte: ketoconazole; matrix: pharmaceutical preparation (injection solution); procedure: high-performance liquid chromatography with ultraviolet detection at 254 nm

Ashraf-Khorassani M, Levy JM; Chromatographia 40: 78-84 (1995). As cited in: Lunn G, Schmuff N; HPLC Methods for Pharmaceutical Analysis. New York, NY: John Wiley & Sons, 1997., p.795

from HSDB

10.2 Clinical Laboratory Methods

HPLC determination in human serum.

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Cambridge, UK: Royal Society of Chemistry, 2013., p. 983

from HSDB

Analyte: ketoconazole; matrix: blood (plasma); procedure: high-performance liquid chromatography with ultraviolet detection at 220 nm; limit of detection: 100-200 ng/mL

von Moltke LL et al; J Pharmacol Exp Ther 276: 370-379 (1996). As cited in: Lunn G, Schmuff N; HPLC Methods for Pharmaceutical Analysis. New York, NY: John Wiley & Sons, 1997., p.792

from HSDB

Analyte: ketoconazole; matrix: blood (serum); procedure: high-performance liquid chromatography with ultraviolet detection at 207 nm; limit of quantitation: 20 ng/mL

Chin TWF et al; Antimicrob Agents Chemother 39: 1671-1675 (1995). As cited in: Lunn G, Schmuff N; HPLC Methods for Pharmaceutical Analysis. New York, NY: John Wiley & Sons, 1997., p.792

from HSDB

Analyte: ketoconazole; matrix: blood (serum); procedure: high-performance liquid chromatography with ultraviolet detection at 226 nm; limit of quantitation: 10 ng/mL

Carver PL et al; Antimicrob Agents Chemother 38: 326-329 (1994). As cited in: Lunn G, Schmuff N; HPLC Methods for Pharmaceutical Analysis. New York, NY: John Wiley & Sons, 1997., p.792

from HSDB

Analyte: ketoconazole; matrix: blood (serum); procedure: high-performance liquid chromatography with ultraviolet detection at 254 nm; limit of quantitation: 200 ng/mL

Piscitelli SC et al; Antimicrob Agents Chemother 35: 1765-1771 (1991). As cited in: Lunn G, Schmuff N; HPLC Methods for Pharmaceutical Analysis. New York, NY: John Wiley & Sons, 1997., p.793

from HSDB

Analyte: ketoconazole; matrix: blood (serum); procedure: high-performance liquid chromatography with ultraviolet detection at 254 nm; limit of quantitation: 50 ng/mL

Turner CA et al; J Antimicrob Chemother 18: 757-763 (1986). As cited in: Lunn G, Schmuff N; HPLC Methods for Pharmaceutical Analysis. New York, NY: John Wiley & Sons, 1997., p.793

from HSDB

Analyte: ketoconazole; matrix: blood (plasma); tissue (lung, liver, adrenal); procedure: high-performance liquid chromatography with ultraviolet detection at 254 nm; limit of detection: 200 ng/mL (plasma), 400 ng/g (tissue)

Riley CM, James MO; J Chromatogr 377: 287-294 (1986). As cited in: Lunn G, Schmuff N; HPLC Methods for Pharmaceutical Analysis. New York, NY: John Wiley & Sons, 1997., p.794

from HSDB

Analyte: ketoconazole; matrix: blood, biological fluid; procedure: high-performance liquid chromatography with ultraviolet detection at 229 nm

Koves EM; J Chromatogr A 692: 103-119 (1995). As cited in: Lunn G, Schmuff N; HPLC Methods for Pharmaceutical Analysis. New York, NY: John Wiley & Sons, 1997., p.796

from HSDB

Analyte: ketoconazole; matrix: tissue (skin); procedure: high-performance liquid chromatography with ultraviolet detection at 254 nm; limit of detection: 50 ng/mL

Pershing LK et al; Antimicrob Agents Chemother 38: 90-95 (1994). As cited in: Lunn G, Schmuff N; HPLC Methods for Pharmaceutical Analysis. New York, NY: John Wiley & Sons, 1997., p.796

from HSDB

11 Safety and Hazards

11.1 Hazards Identification

11.1.1 GHS Classification

Showing 1 of 4 View More

Pictogram(s)	 Acute Toxic, Health Hazard, Environmental Hazard
Signal	Danger
GHS Hazard Statements	H301: Toxic if swallowed [Danger Acute toxicity, oral] H360F ***: May damage fertility [Danger Reproductive toxicity] H373 **: Causes damage to organs through prolonged or repeated exposure [Warning Specific target organ toxicity, repeated exposure] H400: Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard] H410: Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard]
Precautionary Statement Codes	P201, P202, P260, P264, P270, P273, P281, P301+P310, P308+P313, P314, P321, P330, P391, P405, and P501 (The corresponding statement to each P-code can be found at the GHS Classification page.)

from EU REGULATION (EC) No 1272/2008

11.1.2 Fire Hazard

Not combustible.

- from ILO International Chemical Safety Cards (ICSC)

11.1.3 Fire Potential

Not combustible.

International Program on Chemical Safety/European Commission; International Chemical Safety Card (ICSC) on Ketoconazole (65277-42-1), ICSC No. 1700 (Peer Review Status: 02/04/2009, Validated). Available from, as of November 11, 2014: ***http://www.inchem.org/pages/icsc.html***

- from HSDB

11.2 First Aid Measures

11.2.1 Inhalation First Aid

Fresh air, rest.

- from ILO International Chemical Safety Cards (ICSC)

11.2.2 Skin First Aid

Rinse and then wash skin with water and soap.

- from ILO International Chemical Safety Cards (ICSC)

11.2.3 Eye First Aid

Rinse with plenty of water (remove contact lenses if easily possible).

- from ILO International Chemical Safety Cards (ICSC)

11.2.4 Ingestion First Aid

Rinse mouth. Give a slurry of activated charcoal in water to drink. Refer immediately for medical attention.

- from ILO International Chemical Safety Cards (ICSC)

11.3 Fire Fighting

In case of fire in the surroundings, use appropriate extinguishing media.

- from ILO International Chemical Safety Cards (ICSC)

11.3.1 Fire Fighting Procedures

Suitable extinguishing media: Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

Sigma-Aldrich; Material Safety Data Sheet for Ketoconazole. Product Number: UC280, Version 5.1 (Revision Date 06/27/2014). Available from, as of November 11, 2014: ***http://www.sigmaaldrich.com/safety-center.html***

- from HSDB

Advice for firefighters: Wear self contained breathing apparatus for fire fighting if necessary.

Sigma-Aldrich; Material Safety Data Sheet for Ketoconazole. Product Number: UC280, Version 5.1 (Revision Date 06/27/2014). Available from, as of November 11, 2014: ***http://www.sigmaaldrich.com/safety-center.html***

- from HSDB

11.4 Accidental Release Measures

11.4.1 Spillage Disposal

Personal protection: filter respirator for organic gases and particulates adapted to the airborne concentration of the substance. Do NOT let this chemical enter the environment. Sweep spilled substance into covered containers. If appropriate, moisten first to prevent dusting. Carefully collect remainder. Then store and dispose of according to local regulations.

- from ILO International Chemical Safety Cards (ICSC)

11.4.2 Cleanup Methods

Accidental Release Measures. Personal precautions, protective equipment and emergency procedures: Wear respiratory protection. Avoid dust formation. Avoid breathing vapors, mist or gas. Ensure adequate ventilation. Evacuate personnel to safe areas. Avoid breathing dust. Environmental precautions: Prevent further leakage or spillage if safe to do so. Do not let product enter drains. Discharge into the environment must be avoided. Methods and materials for containment and cleaning up: Pick up and arrange disposal without creating dust. Sweep up and shovel. Keep in suitable, closed containers for disposal.

*Sigma-Aldrich; Material Safety Data Sheet for Ketoconazole. Product Number: UC280, Version 5.1 (Revision Date 06/27/2014). Available from, as of November 11, 2014: **http://www.sigmaaldrich.com/safety-center.html***

▸ from HSDB

11.4.3 Disposal Methods

SRP: Expired or waste pharmaceuticals shall carefully take into consideration applicable DEA, EPA, and FDA regulations. It is not appropriate to dispose by flushing the pharmaceutical down the toilet or discarding to trash. If possible return the pharmaceutical to the manufacturer for proper disposal being careful to properly label and securely package the material. Alternatively, the waste pharmaceutical shall be labeled, securely packaged and transported by a state licensed medical waste contractor to dispose by burial in a licensed hazardous or toxic waste landfill or incinerator.

▸ from HSDB

SRP: At the time of review, regulatory criteria for small quantity disposal are subject to significant revision, however, household quantities of waste pharmaceuticals may be managed as follows: Mix with wet cat litter or coffee grounds, double bag in plastic, discard in trash.

▸ from HSDB

Waste treatment methods. Product: Offer surplus and non-recyclable solutions to a licensed disposal company. Contact a licensed professional waste disposal service to dispose of this material. Dissolve or mix the material with a combustible solvent and burn in a chemical incinerator equipped with an afterburner and scrubber. Contaminated packaging: Dispose of as unused product.

*Sigma-Aldrich; Material Safety Data Sheet for Ketoconazole. Product Number: UC280, Version 5.1 (Revision Date 06/27/2014). Available from, as of November 11, 2014: **http://www.sigmaaldrich.com/safety-center.html***

▸ from HSDB

11.4.4 Preventive Measures

Appropriate engineering controls: Avoid contact with skin, eyes and clothing. Wash hands before breaks and immediately after handling the product.

*Sigma-Aldrich; Material Safety Data Sheet for Ketoconazole. Product Number: UC280, Version 5.1 (Revision Date 06/27/2014). Available from, as of November 11, 2014: **http://www.sigmaaldrich.com/safety-center.html***

▸ from HSDB

Precautions for safe handling: Avoid contact with skin and eyes. Avoid formation of dust and aerosols. Provide appropriate exhaust ventilation at places where dust is formed.

*Sigma-Aldrich; Material Safety Data Sheet for Ketoconazole. Product Number: UC280, Version 5.1 (Revision Date 06/27/2014). Available from, as of November 11, 2014: **http://www.sigmaaldrich.com/safety-center.html***

▸ from HSDB

Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

*Sigma-Aldrich; Material Safety Data Sheet for Ketoconazole. Product Number: UC280, Version 5.1 (Revision Date 06/27/2014). Available from, as of November 11, 2014: **http://www.sigmaaldrich.com/safety-center.html***

▸ from HSDB

SRP: Local exhaust ventilation should be applied wherever there is an incidence of point source emissions or dispersion of regulated contaminants in the work area. Ventilation control of the contaminant as close to its point of generation is both the most economical and safest method to minimize personnel exposure to airborne contaminants. Ensure that the local ventilation moves the contaminant away from the worker.

▸ from HSDB

11.5 Handling and Storage

11.5.1 Safe Storage

Provision to contain effluent from fire extinguishing. Well closed. Separated from food and feedstuffs. Store in an area without drain or sewer access.

▸ from ILO International Chemical Safety Cards (ICSC)

11.5.2 Storage Conditions

Store at controlled room temperature 15 deg - 25 deg C (59 deg - 77 deg F). Protect from moisture.

*NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: **http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465***

▸ from HSDB

Ketoconazole topical cream should be stored at a temperature less than 25 deg C and should not be frozen. The cream should not be stored at high temperatures (eg, warmer than 37 deg C), since creams generally separate at these temperatures. Ketoconazole 2% shampoo should be stored at temperatures not exceeding 25 deg C and should be protected from light; the 1% shampoo should be stored between 2-30 deg C and should be protected from light and freezing.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Conditions for safe storage, including any incompatibilities: Keep container tightly closed in a dry and well-ventilated place. Recommended storage temperature: 2 - 8 deg C.

*Sigma-Aldrich; Material Safety Data Sheet for Ketoconazole. Product Number: UC280, Version 5.1 (Revision Date 06/27/2014). Available from, as of November 11, 2014: **http://www.sigmaaldrich.com/safety-center.html***

▸ from HSDB

11.6 Exposure Control and Personal Protection

11.6.1 Inhalation Risk

A harmful concentration of airborne particles can be reached quickly when dispersed, especially if powdered.

▸ from ILO International Chemical Safety Cards (ICSC)

11.6.2 Effects of Long Term Exposure

The substance may have effects on the endocrine system and liver. Animal tests show that this substance possibly causes toxicity to human reproduction or development.

▸ from ILO International Chemical Safety Cards (ICSC)

11.6.3 Personal Protective Equipment (PPE)

Eye/face protection: Face shield and safety glasses Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU).

*Sigma-Aldrich; Material Safety Data Sheet for Ketoconazole. Product Number: UC280, Version 5.1 (Revision Date 06/27/2014). Available from, as of November 11, 2014: **http://www.sigmaaldrich.com/safety-center.html***

▸ from HSDB

Skin protection: Handle with gloves.

*Sigma-Aldrich; Material Safety Data Sheet for Ketoconazole. Product Number: UC280, Version 5.1 (Revision Date 06/27/2014). Available from, as of November 11, 2014: **http://www.sigmaaldrich.com/safety-center.html***

▸ from HSDB

Body Protection: Complete suit protecting against chemicals, The type of protective equipment must be selected according to the concentration and amount of the dangerous substance at the specific workplace.

*Sigma-Aldrich; Material Safety Data Sheet for Ketoconazole. Product Number: UC280, Version 5.1 (Revision Date 06/27/2014). Available from, as of November 11, 2014: **http://www.sigmaaldrich.com/safety-center.html***

▸ from HSDB

Respiratory protection: Where risk assessment shows air-purifying respirators are appropriate use a full-face particle respirator type N100 (US) or type P3 (EN 143) respirator cartridges as a backup to engineering controls. If the respirator is the sole means of protection, use a full-face supplied air respirator. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

*Sigma-Aldrich; Material Safety Data Sheet for Ketoconazole. Product Number: UC280, Version 5.1 (Revision Date 06/27/2014). Available from, as of November 11, 2014: **http://www.sigmaaldrich.com/safety-center.html***

▸ from HSDB

Use local exhaust or breathing protection.

*International Program on Chemical Safety/European Commission; International Chemical Safety Card (ICSC) on Ketoconazole (65277-42-1), ICSC No. 1700 (Peer Review Status: 02/04/2009, Validated). Available from, as of November 11, 2014: **http://www.inchem.org/pages/icsc.html***

▸ from HSDB

11.6.4 Exposure Prevention

STRICT HYGIENE!

- from ILO International Chemical Safety Cards (ICSC)

11.6.5 Inhalation Prevention

Use local exhaust or breathing protection.

- from ILO International Chemical Safety Cards (ICSC)

11.6.6 Skin Prevention

Protective gloves.

- from ILO International Chemical Safety Cards (ICSC)

11.6.7 Eye Prevention

Wear safety goggles.

- from ILO International Chemical Safety Cards (ICSC)

11.6.8 Ingestion Prevention

Do not eat, drink, or smoke during work.

- from ILO International Chemical Safety Cards (ICSC)

11.7 Transport Information

11.7.1 Packaging and Labelling

Do not transport with food and feedstuffs.

- from ILO International Chemical Safety Cards (ICSC)

11.7.2 EC Classification

Symbol: T, N; R: 60-25-48/22-50/53; S: 53-45-60-61; Note: E

- from ILO International Chemical Safety Cards (ICSC)

11.7.3 UN Classification

UN Hazard Class: 6.1; UN Pack Group: III

- from ILO International Chemical Safety Cards (ICSC)

11.8 Regulatory Information

11.8.1 FDA Requirements

The Approved Drug Products with Therapeutic Equivalence Evaluations identifies currently marketed prescription drug products, including ketoconazole, approved on the basis of safety and effectiveness by FDA under sections 505 of the Federal Food, Drug, and Cosmetic Act.

*DHHS/FDA; Electronic Orange Book-Approved Drug Products with Therapeutic Equivalence Evaluations. Available from, as of November 12, 2014: **http://www.fda.gov/cder/ob/***

- from HSDB

The Approved Drug Products with Therapeutic Equivalence Evaluations identifies currently marketed over-the-counter drug products, including ketoconazole, approved on the basis of safety and effectiveness by FDA under sections 505 of the Federal Food, Drug, and Cosmetic Act.

*DHHS/FDA; Electronic Orange Book-Approved Drug Products with Therapeutic Equivalence Evaluations. Available from, as of November 12, 2014: **http://www.fda.gov/cder/ob/***

- from HSDB

11.9 Other Safety Information

11.9.1 Toxic Combustion Products

Special hazards arising from the substance or mixture: Carbon oxides, nitrogen oxides (NOx), **Hydrogen chloride** gas.

Sigma-Aldrich; Material Safety Data Sheet for Ketoconazole. Product Number: UC280, Version 5.1 (Revision Date 06/27/2014). Available from, as of November 11, 2014: ***http://www.sigmaaldrich.com/safety-center.html***

▸ from HSDB

12 Toxicity

12.1 Toxicological Information

12.1.1 Hepatotoxicity

Mild and transient elevations in liver enzymes occur in 4% to 20% of patients on oral ketaconazole. These abnormalities are usually transient and asymptomatic and uncommonly require dose adjustment or discontinuation. Clinically apparent hepatotoxicity from ketaconazole is well described in the literature and is estimated to occur in 1:2,000 to 1:15,000 users. The liver injury typically presents with an acute hepatitis-like picture 1 to 6 months after starting therapy. While most cases present with a hepatocellular pattern of injury, cholestatic forms have been described. Rash, fever and eosinophilia are rare as is autoantibody formation. Recovery upon stopping therapy may be delayed and generally takes 1 to 3 months. Severe cases with acute liver failure and death or need for emergency liver transplantation have been described.

▸ from LiverTox

12.1.2 NIOSH Toxicity Data

▸ from The National Institute for Occupational Safety and Health (NIOSH)

12.1.3 Exposure Routes

The substance can be absorbed into the body by ingestion.

▸ from ILO International Chemical Safety Cards (ICSC)

12.1.4 Inhalation Symptoms

Cough.

▸ from ILO International Chemical Safety Cards (ICSC)

12.1.5 Skin Symptoms

Redness.

▸ from ILO International Chemical Safety Cards (ICSC)

12.1.6 Ingestion Symptoms

Nausea. Headache. Dizziness. Vomiting. Diarrhoea.

▸ from ILO International Chemical Safety Cards (ICSC)

12.1.7 Acute Effects

from ChemIDplus

12.1.8 Interactions

Because gastric acidity is necessary for the dissolution and absorption of ketoconazole, concomitant use of drugs that decrease gastric acid output or increase gastric pH (e.g., antacids, antimuscarinics, **histamine** H2-receptor antagonists, proton-pump inhibitors, **sucralfate**) may decrease absorption of ketoconazole resulting in decreased plasma concentrations of the antifungal. Concomitant use of antacids, antimuscarinics, **histamine** H2-receptor antagonists, proton-pump inhibitors (e.g., **omeprazole**, lanosprazole), or **sucralfate** is not recommended in patients receiving ketoconazole.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Elevated plasma concentrations of **digoxin** have been reported in patients receiving ketoconazole. Although it is unclear whether concomitant use of ketoconazole caused these increased concentrations, **digoxin** concentrations should be monitored closely in patients receiving the antifungal agent.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Like other **imidazole** derivatives, ketoconazole may enhance the anticoagulant effect of **coumarin** anticoagulants. When ketoconazole is used concomitantly with these drugs, the anticoagulant effect should be carefully monitored and dosage of the anticoagulant adjusted accordingly.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Concomitant use of **mefloquine** (single 500-mg dose) and ketoconazole (400 mg once daily for 10 days) in healthy adults increased the mean peak plasma concentration and AUC of **mefloquine** by 64 and 79%, respectively, and increased the mean elimination half-life of **mefloquine** from 322 hours to 448 hours. Because of the risk of a potentially fatal prolongation of the corrected QT (QTc) interval, the manufacturer of **mefloquine** states that ketoconazole should not be used concomitantly with **mefloquine** or within 15 weeks after the last **mefloquine** dose.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Concomitant use of ketoconazole may decrease clearance of **busulfan** resulting in increased systemic exposure to the antineoplastic agent. Careful monitoring, with possible adjustment in dosage, is recommended if **busulfan** and ketoconazole are used concomitantly.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Elevated plasma concentrations of **digoxin** have been reported in patients receiving ketoconazole. Although it is unclear whether concomitant use of ketoconazole caused these increased concentrations, **digoxin** concentrations should be monitored closely in patients receiving the antifungal.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Ketoconazole is a potent inhibitor of CYP3A4, and concomitant use in patients receiving a phosphodiesterase type 5 (PDE5) inhibitor (**sildenafil**, **tadalafil**, **vardenafil**) can substantially increase plasma concentrations of the PDE5 inhibitor and may increase the risk of adverse effects (e.g., hypotension, visual changes, priapism) associated with these agents.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

In a crossover study in healthy individuals, concomitant use of oral **quinine sulfate** (single 500-mg dose; not commercially available in the US) and ketoconazole (100 mg twice daily for 3 days) increased the mean AUC of **quinine** by 45% and decreased clearance of **quinine** by 31% compared with administration of the antimalarial alone. Dosage adjustment of **quinine** is not needed in patients receiving ketoconazole; however, patients should be monitored closely for adverse effects associated with **quinine**.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of **bosentan** and ketoconazole increased peak plasma concentrations and AUC of **bosentan** approximately twofold. Although dosage adjustment of **bosentan** is not needed in patients receiving ketoconazole, close monitoring for increased **bosentan**-associated adverse effects is recommended.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of **buspirone** with ketoconazole may result in clinically important increases in plasma concentrations of **buspirone**. Careful monitoring, with possible dosage adjustment, is recommended if **buspirone** and ketoconazole are used concomitantly. A low initial dose of **buspirone** should be used and subsequent dosage should be adjusted as needed based on clinical assessment.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of **cilostazol** and ketoconazole increases peak plasma concentrations and AUC of **cilostazol** approximately twofold and has increased the incidence of adverse effects associated with the drug (e.g., headache). If **cilostazol** and ketoconazole are used concomitantly, careful monitoring is recommended and a 50% reduction in **cilostazol** dosage should be considered.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Clearance of **docetaxel** in cancer patients is decreased by 50% in the presence of ketoconazole. If **docetaxel** and ketoconazole are used concomitantly, careful monitoring is recommended and a reduction in **docetaxel** dosage may be necessary to minimize the incidence of **docetaxel**-associated toxicities.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of ergot alkaloids (e.g., **ergotamine**, **dihydroergotamine**) and ketoconazole is contraindicated. Concomitant use of the drugs may increase concentrations of the ergot alkaloid resulting in ergotism (i.e., risk for vasospasm potentially leading to cerebral ischemia and/or ischemia of the extremities).

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of **boceprevir** (single 400-mg dose) with ketoconazole (400 mg twice daily for 8 days) increases **boceprevir** plasma concentrations and AUC and may increase ketoconazole concentrations. If ketoconazole is required in patients receiving **boceprevir**, ketoconazole dosage should not exceed 200 mg daily. Concomitant use of **telaprevir** (single 750-mg dose) and ketoconazole (single 400-mg dose) increases **telaprevir** plasma concentrations and AUC and may increase ketoconazole concentrations. If ketoconazole is required in patients receiving **telaprevir**, ketoconazole dosage should not exceed 200 mg daily.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of ketoconazole and **atorvastatin** or **lovastatin** is contraindicated. Concomitant use of **hydroxymethylglutaryl-CoA** (**HMG-CoA**) reductase inhibitors (statins) metabolized by CYP3A (e.g., **atorvastatin**, **lovastatin**) and ketoconazole may increase plasma concentrations of the statin resulting in increased effects and increased risk of statin-associated adverse effects, including myopathy and rhabdomyolysis.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of ketoconazole and **sirolimus** is not recommended since peak plasma concentrations and AUC of **sirolimus** are increased approximately 4-fold and 11-fold, respectively.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of ketoconazole and **tacrolimus** may affect metabolism of **tacrolimus** resulting in increased plasma concentrations of the immunosuppressive agent. Careful monitoring, with possible dosage adjustment, is recommended if ketoconazole and **tacrolimus** are used concomitantly.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

In vitro studies indicate that ketoconazole can inhibit the metabolism of **paclitaxel**. Although this potential pharmacokinetic interaction has not been evaluated in humans, **paclitaxel** and ketoconazole should be used concomitantly with caution and careful monitoring.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of **pimozide** and ketoconazole is contraindicated. Concomitant use of the drugs may increase **pimozide** plasma concentrations and lead to QTc interval prolongation, sometimes resulting in serious life-threatening ventricular tachyarrhythmias such as torsades de pointes.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Ketoconazole decreases apparent oral clearance of **tolterodine** resulting in at least a twofold increase in **tolterodine** concentrations. Careful monitoring, with possible dosage adjustment, is recommended if **tolterodine** and ketoconazole are used concomitantly. If **tolterodine** is initiated in a patient already receiving ketoconazole, initial dosage of the drug should be reduced by 50%.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of ketoconazole and **theophylline** has resulted in decreased serum **theophylline** concentrations in a limited number of patients. Data from a study in healthy adults, however, indicate that single or multiple oral doses of ketoconazole may not substantially alter the plasma clearance of single IV doses of **theophylline** (as **aminophylline**). Pending further accumulation of data, serum **theophylline** concentrations and the patient should be monitored closely and **theophylline** dosage adjusted accordingly when ketoconazole is initiated or discontinued in patients receiving **theophylline**.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Ketoconazole is a substrate for and potent inhibitor of cytochrome P-450 (CYP) isoenzyme 3A4. Concomitant use of ketoconazole with drugs that are metabolized by CYP3A4 may increase plasma concentrations of the drugs and may increase or prolong therapeutic and/or adverse effects associated with the drugs. Concomitant use of ketoconazole with drugs that inhibit CYP3A4 may increase plasma concentrations of ketoconazole and increase the risk of adverse effects associated with the antifungal. Concomitant use of ketoconazole with drugs that induce CYP3A4 may decrease plasma concentrations of ketoconazole and may decrease efficacy of the antifungal.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of ketoconazole and **alprazolam**, **midazolam**, or **triazolam** increases peak plasma concentrations of these benzodiazepines and may result in potentiated and prolonged hypnotic and sedative effects, especially in patients receiving repeated or chronic therapy with the drugs. Concomitant use of ketoconazole and **alprazolam**, oral **midazolam**, or oral **triazolam** is contraindicated. Because the sedative effects may be prolonged, special precaution and patient monitoring is required if parenteral **midazolam** is used in patients receiving ketoconazole.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of ketoconazole and **amlodipine**, **felodipine**, **nicardipine**, **nifedipine**, or **verapamil** results in increased plasma concentrations of the **calcium**-channel blocker. If ketoconazole and one of these **calcium**-channel blockers is used concomitantly, caution and careful monitoring, with possible dosage adjustment, is recommended. Concomitant use of **nisoldipine** and ketoconazole is contraindicated. Pretreatment with and concomitant use of ketoconazole has resulted in an 11-fold increase in peak plasma concentrations and a 24-fold increase in the AUC of **nisoldipine**.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of **dofetilide** and ketoconazole is contraindicated. Concomitant use of the drugs may increase **dofetilide** plasma concentrations and lead to QTc interval prolongation, sometimes resulting in serious life-threatening ventricular tachyarrhythmias such as torsades de pointes.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of ketoconazole and **cyclosporine** has been reported to increase plasma concentrations of **cyclosporine** and serum **creatinine** concentrations. It has been suggested that ketoconazole may interfere with the metabolism of **cyclosporine** via hepatic microsomal enzyme inhibition, although other mechanisms may also be involved. Careful monitoring, with possible dosage adjustment, is recommended if ketoconazole and **cyclosporine** are used concomitantly. When ketoconazole therapy is initiated in a patient receiving **cyclosporine**, renal function and blood or plasma **cyclosporine** concentrations should be monitored; reduction in **cyclosporine** dosage or replacement of **cyclosporine** with another immunosuppressive agent should be considered. Patients stabilized on both drugs may require an increase in **cyclosporine** dosage when ketoconazole is discontinued.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

In a limited number of individuals receiving ketoconazole dosages of 200 mg twice daily, concomitant administration of a single 20-mg dose of **loratadine** resulted in a 302% average increase of **loratadine**'s AUC, a 251% average increase in peak **loratadine** plasma concentrations, a 155% average increase of **descarboethoxyloratadine**'s (an active metabolite of **loratadine**) AUC, and a 141% average increase in peak **descarboethoxyloratadine** plasma concentrations compared with those achieved in individuals receiving **loratadine** and placebo. No changes in the QTc intervals were reported 2, 6, and 24 hours after concomitant administration of the drugs and adverse effects were similar in individuals receiving **loratadine** concomitantly with ketoconazole and in those receiving **loratadine** and placebo.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

In vitro data suggest that **alfentanil**, **fentanyl**, and **sufentanil** are metabolized by CYP3A4. Therefore, concomitant use of ketoconazole may increase plasma concentrations of these opiate agonists. Careful monitoring, with possible dosage adjustment, is recommended if ketoconazole is used concomitantly with **alfentanil**, **fentanyl**, or **sufentanil**.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

The manufacturer of ketoconazole recommends that the initial dose of **sildenafil** be reduced by 50% in patients receiving ketoconazole. The manufacturer of **sildenafil** states that the initial dose of **sildenafil** should be 25 mg in patients receiving ketoconazole.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Concomitant use of ketoconazole (400 mg daily) and **tadalafil** (20 mg) results in a 312% increase in the **tadalafil** AUC and a 22% increase in peak **tadalafil** plasma concentrations; concomitant use of ketoconazole (200 mg daily) and **tadalafil** (10 mg) results in a 107% increase in the **tadalafil** AUC and a 15% increase in peak **tadalafil** plasma concentrations. The manufacturer of **tadalafil** recommends that patients receiving ketoconazole receive no more than 10 mg of **tadalafil** once every 72 hours. If a once-daily **tadalafil** regimen is used, those receiving ketoconazole should receive no more than 2.5 mg of **tadalafil** once daily.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Concomitant use of ketoconazole (200 mg once daily) and **vardenafil** (5 mg) results in a 10-fold increase in the AUC of **vardenafil** and a 4-fold increase in peak plasma concentrations of **vardenafil**. The manufacturer of **vardenafil** recommends that patients receiving ketoconazole in a dosage of 400 mg daily should receive no more than a single 2.5-mg dose of **vardenafil** in a 24-hour period and those receiving ketoconazole in a dosage of 200 mg daily should receive no more than a single 5-mg dose of **vardenafil** in a 24-hour period. 3

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Concomitant use of **telithromycin** and ketoconazole may increase the AUC of **telithromycin** and increase the risk for **telithromycin**-associated adverse events. Careful monitoring, with possible dosage adjustment, is recommended if **telithromycin** and ketoconazole are used concomitantly.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Because ketoconazole is a potent inhibitor of CYP34A,380 381 concomitant use with **trazodone** may result in substantially increased plasma **trazodone** concentrations with the potential for adverse effects. If **trazodone** is used in patients receiving ketoconazole, consider reducing **trazodone** dosage.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

In vitro data suggest that **trimetrexate** is extensively metabolized by CYP3A4 and in vitro animal models have demonstrated that ketoconazole potently inhibits metabolism of **trimetrexate**. If **trimetrexate** and ketoconazole are used concomitantly, patients should be carefully monitored for **trimetrexate**-associated toxicities; dosage adjustments may be needed.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Ketoconazole may inhibit metabolism of vinca alkaloids metabolized by CYP3A4.263 384 If ketoconazole and **vincristine**, **vinblastine**, or **vinorelbine** are used concomitantly, the patient should be monitored closely for vinca alkaloid toxicity; dosage adjustments may be needed.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

Concomitant use of **eplerenone** and ketoconazole is contraindicated. Concomitant use of the drugs increases the AUC of **eplerenone** approximately fivefold and increases the risk of hyperkalemia and hypotension.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of **quinidine** and ketoconazole is contraindicated. Concomitant use of the drugs may increase **quinidine** plasma concentrations and lead to QTc interval prolongation, sometimes resulting in serious life-threatening ventricular tachyarrhythmias such as torsades de pointes.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Severe hypoglycemia has been reported when **miconazole** (a systemic **imidazole** no longer commercially available in the US) was used concomitantly with an oral **sulfonylurea** antidiabetic agent. Because ketoconazole is structurally related to **miconazole**, the possibility that this interaction could occur with ketoconazole should be considered.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of ketoconazole and **delavirdine** may result in increased trough plasma concentrations of **delavirdine**. Concomitant use of **efavirenz** and ketoconazole may result in decreased ketoconazole plasma concentrations. Concomitant use of **etravirine** and ketoconazole may result in increased **etravirine** plasma concentrations and decreased ketoconazole plasma concentrations. Dosage adjustment of ketoconazole may be needed depending on other concomitantly administered drugs. Ketoconazole and **nevirapine** should not be used concomitantly since plasma concentrations and AUC of the antifungal are decreased and efficacy may be reduced. Concomitant use of ketoconazole and **rilpivirine** has resulted in increased **rilpivirine** plasma concentrations and AUC and decreased ketoconazole plasma concentrations and AUC. **Rilpivirine** dosage adjustments are not needed when the drug is used concomitantly with ketoconazole; however, patients should be monitored for breakthrough fungal infections.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Clinically important changes in **atazanavir** plasma concentrations or AUC do not occur if **atazanavir** (without low-dose **ritonavir**) is used concomitantly with ketoconazole. Concomitant use of **ritonavir**-boosted **darunavir** and ketoconazole increases **darunavir** and ketoconazole concentrations. Ketoconazole dosage should not exceed 200 mg daily in patients receiving **ritonavir**-boosted **darunavir**. Concomitant use of ketoconazole and **fosamprenavir** (with or without low-dose **ritonavir**) may result in increased concentrations of the antifungal. In patients receiving **fosamprenavir** (without low-dose **ritonavir**), reduced antifungal dosage may be needed in those receiving ketoconazole dosages exceeding 400 mg daily. Ketoconazole dosage should not exceed 200 mg daily in those receiving **ritonavir**-boosted **fosamprenavir**. Concomitant use of ketoconazole and **indinavir** can increase **indinavir** concentrations. Dosage of **indinavir** should be reduced to 600 mg every 8 hours in patients receiving ketoconazole. Concomitant use of the fixed combination of **lopinavir** and **ritonavir** (**lopinavir/ritonavir**) and ketoconazole results in increased concentrations of the antifungal. Ketoconazole dosage should not exceed 200 mg daily in patients receiving **lopinavir/ritonavir**. Concomitant use of ketoconazole (400 mg once daily for 7 days) and **nelfinavir** (500 mg 3 times daily for 5-6 days) resulted in a 35% increase in the AUC and a 25% increase in peak plasma concentrations of **nelfinavir**. Concomitant use of **ritonavir**-boosted **saquinavir** and ketoconazole increases concentrations of ketoconazole, but does not appear to affect **saquinavir** pharmacokinetics. Ketoconazole dosage should not exceed 200 mg daily in patients receiving **ritonavir**-boosted **saquinavir**. Concomitant use of **ritonavir**-boosted **tipranavir** and ketoconazole may result in increased ketoconazole concentrations. Ketoconazole and **ritonavir**-boosted **tipranavir** should be used concomitantly with caution and ketoconazole dosage should not exceed 200 mg daily.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Disulfiram reactions, including flushing, rash, peripheral edema, nausea, and headache, have occurred rarely in patients who ingested alcohol while receiving ketoconazole therapy; symptoms usually resolved within a few hours. Patients should be advised to avoid alcohol consumption during ketoconazole therapy. Some clinicians recommend that alcohol be avoided during and for 48 hours after discontinuance of ketoconazole.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Because ketoconazole can cause severe hepatotoxicity, concomitant use with other potentially hepatotoxic drugs should be avoided if possible.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of ketoconazole and **methylprednisolone** or **prednisolone** may increase plasma concentrations of the corticosteroid, possibly due to decreased clearance. Ketoconazole may enhance the adrenal suppressive effects of corticosteroids. Patients should be carefully monitored and dosage adjustment of the corticosteroid may be needed when ketoconazole is used concomitantly with **methylprednisolone** or **prednisolone**.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of ketoconazole and **cisapride** (available in the US only under a limited-use protocol) is contraindicated. Ketoconazole potentially inhibits metabolism of **cisapride**. Concomitant use of ketoconazole and **cisapride** has resulted in

increased **cisapride** plasma concentrations and AUC; QT interval prolongation and serious cardiovascular effects, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes, have been reported rarely.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of **maraviroc** and ketoconazole may result in substantial increases in the AUC of **maraviroc**. If **maraviroc** is used concomitantly with ketoconazole, **maraviroc** dosage should be reduced to 150 mg twice daily.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of **rifabutin** and ketoconazole decreases plasma concentrations of ketoconazole and may increase plasma concentrations of **rifabutin**. Concomitant use of **rifampin** and ketoconazole decreases plasma concentrations of the antifungal. In one patient receiving ketoconazole concomitantly with **rifampin** and **isoniazid**, serum concentrations of both **rifampin** and ketoconazole were decreased. Although administration of ketoconazole 12 hours after the **rifampin** dose resulted in therapeutic serum concentrations of **rifampin**, serum concentrations of ketoconazole were subtherapeutic regardless of when the doses were given. In addition, **isoniazid** and **rifampin** appeared to have an additive effect in reducing serum ketoconazole concentrations. Concomitant use of ketoconazole and **rifampin**, **rifabutin**, or **isoniazid** is not recommended.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of ketoconazole and drugs that are CYP3A4 substrates that prolong the QT interval (e.g., **cisapride**, **dofetilide**, **pimozide**, **quinidine**) may increase plasma concentrations of the concomitantly administered CYP3A4 substrate, which can lead to QT interval prolongation, sometimes resulting in life-threatening ventricular dysarrhythmias such as torsades de pointes. Concomitant use of ketoconazole and these drugs that prolong the QT interval is contraindicated.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of ketoconazole with **carbamazepine** or **phenytoin** may increase plasma concentrations of the antifungal and/or the anticonvulsant. Concomitant use of ketoconazole and **carbamazepine** or **phenytoin** is not recommended. If the drugs are used concomitantly, plasma concentrations of the anticonvulsant should be closely monitored and the patient should be monitored for decreased ketoconazole efficacy.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

Concomitant use of the fixed combination of **artemether** and **lumefantrine** (**artemether**/**lumefantrine**) and ketoconazole increases peak plasma concentrations and area under the plasma concentration-time curve (AUC) of **artemether**, the active metabolite of **artemether** (**dihydroartemisinin**; DHA), and **lumefantrine**. Although adjustment of **artemether**/**lumefantrine** dosage is not necessary if ketoconazole is used concomitantly, ketoconazole and **artemether**/**lumefantrine** should be used concomitantly with caution because of the potential for increased **lumefantrine** concentrations and increased risk of QT interval prolongation.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

From 2006 to 2010, ketoconazole was given in 199 patients and was continued for at least 1 year or until graft failure (Group 1), while 149 patients did not receive any ketoconazole (Group 2). A combination of **tacrolimus**, **mycophenolate** and steroid was used as maintenance therapy. High risk patients received basiliximab induction. Basic demographic data was similar between the 2 groups. The 5-year cumulative incidence of biopsy-confirmed and clinically-treated acute rejection was significantly higher in Group 1 than in Group 2 (34% vs 18%, P = 0.01). The 5-year Kaplan-Meier estimated graft survival (74.3% vs 76.4%, P = 0.58) and patient survival (87.8% vs 87.5%, P = 0.93) were not different between the 2 groups. Multivariable analyses identified ketoconazole usage as an independent risk of acute rejection (HR = 2.33, 95%CI: 1.33-4.07; P = 0.003) while **tacrolimus** dose in the 2(nd) month was protective (HR = 0.89, 95%CI: 0.75-0.96; P = 0.041). Co-administration of ketoconazole and **tacrolimus** is associated with significantly higher incidence of acute rejection in kidney transplant recipients. **PubMed Abstract** Full text: **PMC4202487**

Khan E et al; World J Nephrol 3 (3): 107-13 (2014)

▸ from HSDB

Apixaban is an orally active inhibitor of coagulation factor Xa and is eliminated by multiple pathways, including renal and non-renal elimination. Non-renal elimination pathways consist of metabolism by cytochrome P450 [CYP] enzymes, primarily CYP3A4, as well as direct intestinal excretion. Two single-sequence studies evaluated the effect of ketoconazole (a strong dual inhibitor of CYP3A4 and P-glycoprotein [P-gp]) and **diltiazem** (a moderate CYP3A4 inhibitor and a P-gp inhibitor) on **apixaban** pharmacokinetics in healthy subjects. In the ketoconazole study, 18 subjects received **apixaban** 10 mg on days 1 and 7, and ketoconazole 400 mg once daily (qd) on days 4-9. In the **diltiazem** study, 18 subjects received **apixaban** 10 mg on days 1 and 11, and **diltiazem** 360 mg qd on days 4-13. **Apixaban** maximum plasma concentration and area under the plasma concentration-time curve extrapolated to infinity increased by 62% (90% confidence interval [CI], 47-78%) and 99% (90% CI, 81-118%), respectively, with co-administration of ketoconazole, and by 31% (90% CI, 16-49%) and 40% (90% CI, 23-59%), respectively, with **diltiazem**. A 2-fold and 1.4-fold increase in **apixaban** exposure was observed with co-administration of ketoconazole and **diltiazem**, respectively.[Frost CE et al; Br J Clin Pharmacol. 2014 Nov 6. doi: 10.1111/bcp.12541. **PubMed Abstract** Full text: **PMC4415720**

Epub ahead of print]

from HSDB

12.1.9 Toxicity Summary

IDENTIFICATION AND USE: Ketokonazole is used as antifungal medication. HUMAN EXPOSURE AND TOXICITY: Transient increases in serum AST, ALT, and alkaline phosphatase concentrations may occur during ketoconazole therapy. Serious hepatotoxicity has occurred in patients receiving oral ketoconazole, including cases that were fatal or required liver transplantation. Hepatotoxicity may be hepatocellular (in most cases), cholestatic, or a mixed pattern of injury. Although ketoconazole-induced hepatotoxicity usually is reversible following discontinuance of the drug, recovery may take several months and rarely death has occurred. Symptomatic hepatotoxicity usually is apparent within the first few months of ketoconazole therapy, but occasionally may be apparent within the first week of therapy. Some patients with ketoconazole-induced hepatotoxicity had no obvious risk factors for liver disease. Serious hepatotoxicity has been reported in patients receiving high oral ketoconazole dosage for short treatment durations and in patients receiving low oral dosage of the drug for long durations. Many of the reported cases of hepatotoxicity occurred in patients who received the drug for the treatment of tinea unguium (onychomycosi or the treatment of chronic, refractory dermatophytoses. Ketoconazole-induced hepatitis has been reported in some children. Usual dosages (ie, 200-400 mg daily) of ketoconazole have been reported to transiently (for 2-12 hours) inhibit testicular **testosterone** synthesis. A compensatory increase in serum luteinizing hormone (LH) concentrations may occur. Dosages of 800-1200 mg daily have been reported to have a more prolonged effect on **testosterone** synthesis; in one study in males receiving these high dosages, serum **testosterone** concentrations remained at a subnormal level (ie, less than 300 ng/dL) throughout the day in about 30% of those receiving 800 mg daily and in all of those receiving 1200 mg daily. Oligospermia, decreased libido, and impotence often occurred in these males and azoospermia occurred rarely. The drug apparently directly inhibits synthesis of adrenal steroids and **testosterone** in vitro and in vivo. Ketoconazole appears to inhibit steroid synthesis principally by blocking several P-450 enzyme systems (eg, 11beta-hydroxylase, C-17,20-lyase, **cholesterol** side-chain cleavage enzyme). Overall the results show that many of the commonly used **azole** fungicides act as endocrine disruptors in vivo, although the profile of action in vivo varies. As ketoconazole is known to implicate numerous endocrine-disrupting effects in humans. ANIMAL STUDIES: After oral administration toxicity was manifested in mice, rats and guinea pigs by sedation, catalepsy, ataxia, tremors, convulsions and pre-lethal loss of the righting reflex at doses >320 mg/kg. In dogs, toxicity was manifested by diarrhea and vomiting at doses >80 mg/kg. Ketoconazole has been administered by the oral (gavage) and intravenous routes to mice, rats, guinea pigs and dogs. Toxicity after intravenous administration was manifested by spasms, convulsions and dyspnea in rats, mice and guinea pigs; pre-lethal loss of the righting reflex occurred in mice and guinea pigs, and dogs. Toxicity in dogs was also manifested by licking and convulsions. In rats the overall incidence of and type of tumors was not significantly different between treated and control groups, except for high-dosed female rats who had a decrease of the overall tumor rate. In developmental studies in rats the incidence of stillborn fetuses increased from a control value of 0.5% to 32.7% in rats dosed with 40 mg/kg and cannibalization of young occurred in two litters. In mice a significant decline in sperm motility and density in cauda epididymis was noted. A sharp decline in fertility (50% negative) in ketoconazole treated mice was observed. A significant reduction in the total protein and sialic acid contents of testes, epididymis, seminal vesicle and ventral prostate were noticed. The **cholesterol** contents of testes were raised while **fructose** contents of seminal vesicle were reduced significantly. The ketoconazole treatment altered the biochemical milieu of the reproductive tract. In the rabbit, ketoconazole produces evidence of maternal toxicity, embryotoxicity and teratogenicity at a high dose of 40 mg/kg/day. Ketoconazole did not show any signs of mutagenic potential when evaluated using the dominant lethal mutation test or the Ames Salmonella microsomal activator assay. ECOTOXICITY STUDIES: Ketoconazole induced CYP1A and CYP3A expression in rainbow trout. However, the most pronounced effect of ketoconazole was a 60 to 90% decrease in CYP3A catalytic activities in rainbow trout and in killifish.

from HSDB

12.1.10 Antidote and Emergency Treatment

/SRP:/ Immediate first aid: Ensure that adequate decontamination has been carried out. If patient is not breathing, start artificial respiration, preferably with a demand valve resuscitator, bag-valve-mask device, or pocket mask, as trained. Perform CPR if necessary. Immediately flush contaminated eyes with gently flowing **water**. Do not induce vomiting. If vomiting occurs, lean patient forward or place on the left side (head-down position, if possible) to maintain an open airway and prevent aspiration. Keep patient quiet and maintain normal body temperature. Obtain medical attention. /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3rd revised edition, Elsevier Mosby, St. Louis, MO 2007, p. 160

from HSDB

/SRP:/ Basic treatment: Establish a patent airway (oropharyngeal or nasopharyngeal airway, if needed). Suction if necessary. Watch for signs of respiratory insufficiency and assist ventilations if needed. Administer **oxygen** by nonrebreather mask at 10 to 15 L/min. Monitor for pulmonary edema and treat if necessary ... . Monitor for shock and treat if necessary ... . Anticipate seizures and treat if necessary ... . For eye contamination, flush eyes immediately with **water**. Irrigate each eye continuously with 0.9% saline (NS) during transport ... . Do not use emetics. For ingestion, rinse mouth and administer 5 mL/kg up to 200 mL of **water** for dilution if the patient can swallow, has a strong gag reflex, and does not drool ... . Cover skin burns with dry sterile dressings after decontamination ... . /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3rd revised edition, Elsevier Mosby, St. Louis, MO 2007, p. 160

from HSDB

/SRP:/ Advanced treatment: Consider orotracheal or nasotracheal intubation for airway control in the patient who is unconscious, has severe pulmonary edema, or is in severe respiratory distress. Positive-pressure ventilation techniques with a bag valve mask device may be beneficial. Consider drug therapy for pulmonary edema ... . Consider administering a beta

agonist such as **albuterol** for severe bronchospasm ... . Monitor cardiac rhythm and treat arrhythmias as necessary ... . Start IV administration of D5W TKO /SRP: "To keep open", minimal flow rate/. Use 0.9% saline (NS) or lactated Ringer's (LR) if signs of hypovolemia are present. For hypotension with signs of hypovolemia, administer fluid cautiously. Watch for signs of fluid overload ... . Treat seizures with **diazepam** or **lorazepam** ... . Use **proparacaine hydrochloride** to assist eye irrigation ... . /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3rd revised edition, Elsevier Mosby, St. Louis, MO 2007, p. 160-1

▸ from HSDB

In the event of acute accidental overdose, treatment consists of supportive and symptomatic measures. Within the first hour after ingestion, activated **charcoal** may be administered.

*NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: **http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465***

▸ from HSDB

12.1.11 Human Toxicity Excerpts

/HUMAN EXPOSURE STUDIES/ Dosages of 800-1200 mg daily have been reported to have a more prolonged effect on **testosterone** synthesis; in one study in males receiving these high dosages, serum **testosterone** concentrations remained at a subnormal level (ie, less than 300 ng/dL) throughout the day in about 30% of those receiving 800 mg daily and in all of those receiving 1200 mg daily. Oligospermia, decreased libido, and impotence often occurred in these males and azoospermia occurred rarely.

McEvoy, G.K. (ed.). American Hospital Formulary Service. AHFS Drug Information. American Society of Health-System Pharmacists, Bethesda, MD. 2006., p. 523

▸ from HSDB

/SIGNS AND SYMPTOMS/ Transient increases in serum AST, ALT, and alkaline phosphatase concentrations may occur during ketoconazole therapy. Serious hepatotoxicity has occurred in patients receiving oral ketoconazole, including cases that were fatal or required liver transplantation. Hepatotoxicity may be hepatocellular (in most cases), cholestatic, or a mixed pattern of injury. Although ketoconazole-induced hepatotoxicity usually is reversible following discontinuance of the drug, recovery may take several months and rarely death has occurred. Symptomatic hepatotoxicity usually is apparent within the first few months of ketoconazole therapy, but occasionally may be apparent within the first week of therapy. Some patients with ketoconazole-induced hepatotoxicity had no obvious risk factors for liver disease. Serious hepatotoxicity has been reported in patients receiving high oral ketoconazole dosage for short treatment durations and in patients receiving low oral dosage of the drug for long durations. Many of the reported cases of hepatotoxicity occurred in patients who received the drug for the treatment of tinea unguium (onychomycosi or the treatment of chronic, refractory dermatophytoses. Ketoconazole-induced hepatitis has been reported in some children.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

/SIGNS AND SYMPTOMS/ Concomitant use of **pimozide** and ketoconazole is contraindicated. Concomitant use of the drugs may increase **pimozide** plasma concentrations and lead to QTc interval prolongation, sometimes resulting in serious life-threatening ventricular tachyarrhythmias such as torsades de pointes.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

/SIGNS AND SYMPTOMS/ Concomitant use of **dofetilide** and ketoconazole is contraindicated. Concomitant use of the drugs may increase **dofetilide** plasma concentrations and lead to QTc interval prolongation, sometimes resulting in serious life-threatening ventricular tachyarrhythmias such as torsades de pointes.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

/SIGNS AND SYMPTOMS/ Concomitant use of **quinidine** and ketoconazole is contraindicated. Concomitant use of the drugs may increase **quinidine** plasma concentrations and lead to QTc interval prolongation, sometimes resulting in serious life-threatening ventricular tachyarrhythmias such as torsades de pointes.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

/SIGNS AND SYMPTOMS/ Concomitant use of ketoconazole and **cisapride** (available in the US only under a limited-use protocol) is contraindicated. Ketoconazole potentially inhibits metabolism of **cisapride**. Concomitant use of ketoconazole and **cisapride** has resulted in increased **cisapride** plasma concentrations and AUC; QT interval prolongation and serious cardiovascular effects, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes, have been reported rarely.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ from HSDB

/CASE REPORTS/ We present the case of a female patient in whom acute overt hepatitis developed after 60 days of ketoconazole administration (200 mg/day). A prompt renewed hepatic injury 48 hours after an unintentional rechallenge 30

months later provided definitive evidence for a causative relationship between ketoconazole and acute liver injury. Histological examination revealed acute hepatitis with bridging hepatic necrosis. Clinicians should be aware of this cause and effect relationship between ketoconazole and acute liver injury, which can result in prompt severe acute liver injury after rechallenge. PubMed Abstract

Chien RN et al; Int J Clin Pract 57 (9): 829-30 (2003)

from HSDB

/CASE REPORTS/ Ketoconazole is not known to be proarrhythmic without concomitant use of QT interval-prolonging drugs. We report a woman with coronary artery disease who developed a markedly prolonged QT interval and torsades de pointes (TdP) after taking ketoconazole for treatment of fungal infection. Her QT interval returned to normal upon withdrawal of ketoconazole. Genetic study did not find any mutation in her genes that encode cardiac IKr channel proteins. We postulate that by virtue of its direct blocking action on IKr, ketoconazole alone may prolong QT interval and induce TdP. This calls for attention when ketoconazole is administered to patients with risk factors for acquired long QT syndrome. PubMed Abstract

Mok NS et al; J Cardiovasc Electrophysiol 16 (12): 1375-7 (2005)

from HSDB

/CASE REPORTS/ Five cases (four females, one male) of ketoconazole-related liver damage are presented, two of whom died. All patients received ketoconazole (400 mg/day) for various mycoses. In the four women the first signs of hepatotoxicity appeared after four weeks of therapy. One fatal case developed massive necrosis with fulminant liver failure and the other, submassive necrosis. In four cases cholestasis was a prominent finding. Biochemical evidence of biliary stasis may persist for several months, as occurred in the three surviving patients of our series. The two fatal cases continued receiving the drug in spite of its adverse effects. Consequently, repeated evaluation is recommended to detect early signs of liver environment. PubMed Abstract

Findor JA et al; Medicina (B Aires) 58 (3): 277-81 (1998)

from HSDB

/CASE REPORTS/ The most serious side effect of ketoconazole is hepatitis, which has proved fatal in seven reported cases. We present a case of fulminant hepatic failure in a 45-year-old Oriental woman that probably would have been fatal except for a successful liver transplant. A review of the literature of fatalities associated with ketoconazole is presented. PubMed Abstract

Knight TE et al; J Am Acad Dermatol 25 (2 Pt 2): 398-400 (1991)

from HSDB

/CASE REPORTS/ We describe a previously healthy woman who developed liver cirrhosis as a sequela of acute hepatic injury that was induced by ketoconazole administration to treat onychomycosis. The initial presentation of the disease was of a typical acute hepatitis, characterized by nausea, anorexia, fatigue, and jaundice that developed during the administration of ketoconazole. Many other causes of hepatitis were absent in the patient. Even though the hepatic injury was gradually resolved for several months after cessation of the drug, the liver function was not completely restored. Six months after the onset of illness, a follow-up abdominal computed tomography and peritoneoscopic liver biopsy were performed. They revealed a marked reduction in the liver volume and a definite cirrhotic change, which persisted for more than 5 years. The case suggests that the administration of ketoconazole can cause liver cirrhosis through acute hepatic injury within a short time under certain circumstances. PubMed Abstract

Kim TH et al; J Gastroenterol Hepatol 18 (12): 1426-9 (2003)

from HSDB

/CASE REPORTS/ Ketoconazole is a member of a newer group of **imidazole** antifungals. Except for treatment of oral candidiasis, there is no reported experience of use in neonates. Thus, its use in neonatalogy must be considered experimental. Herein we report a major eosinophilia in a very low birth weight neonate induced by transcutaneous resorption of topical ketoconazole. A 26 week premature was intubated and ventilated for a hyaline membrane disease. At more than 2 weeks, he developed diaper dermatitis with Candida albicans. Treatment consisted of local application of ketoconazole. After 6 days of application, WBC showed a major eosinophilia [20,000/uL]. Discontinuation of the drug was followed by a prompt normalization of the eosinophil count. The challenge test by topical ketoconazole reproduced eosinophilia, implicating this drug, which, to our knowledge, has not been described previously to cause eosinophilia in very low weight neonates. Peripheral eosinophilia is an uncommon finding present in a relatively limited number of conditions in children. A minor eosinophilia often seen in premature neonates may in part be due to intubation. This case illustrates the potential danger of percutaneous application of drugs in newborn and infants as it has previously been pointed out way various chemicals. Any deterioration of the corneal layer such as observed in many dermatosis prompts an increase in the cutaneous permeability. Immaturity of the premature skin may have aiso played a role. ... PubMed Abstract

Michel JL et al; Ann Dermatol Venereol 127 (4): 405-7 (2000)

from HSDB

/CASE REPORTS/ ... A 72-year-old woman received antifungal therapy for her almost completely occluded cornea infected with Candida albicans. She was initially prescribed oral ketoconazole 200 mg twice daily. She developed hypotension over the first 2 days of therapy (BP 136/82 mm Hg at baseline; 90/50 mm Hg on day 2). Severe hypotension (BP 90/49 mm Hg) unresponsive to fluid therapy or high-dose **dopamine** developed on day 4 of therapy. An invasive Swan-Ganz catheterization study showed a very low level of peripheral vascular resistance with high cardiac output index without clinical signs of infection. When laboratory tests showed a high level of plasma tryptase, anaphylactic redistribution shock was diagnosed. Her vital signs became more stable after treatment with **hydrocortisone** and **epinephrine** infusion. She was discharged in good condition after 24 hours of observation. ... The events of hypotension were strongly associated with the intake of ketoconazole. The hemodynamic results obtained with Swan-Ganz catheterization were compatible with

anaphylactic shock. The Naranjo probability scale showed a probable association of the adverse event with ketoconazole. Ketoconazole may cause severe anaphylactic shock even when taken orally. Invasive catheterization and elevated tryptase levels can provide important information in the management of anaphylactic shock PubMed Abstract

Liu PY et al; Ann Pharmacother 39 (3): 547-50 (2005)

from HSDB

/EPIDEMIOLOGY STUDIES/ The concentration of intratesticular testosterone (IT-T) required for human spermatogenesis is unknown because spermatogenesis can persist despite the markedly reduced IT-T concentrations observed with LH suppression. Methods to lower IT-T further are needed to determine the relationship between IT-T and spermatogenesis.The objective of the study was to determine the effect of inhibiting the synthesis and metabolism of testosterone (T) on IT-T in gonadotropin-suppressed human testes. Forty normal men participated in a blinded, placebo-controlled, randomized trial at an academic center. All men were first administered the GnRH antagonist acyline to suppress LH. Forty-eight hours after acyline administration, subjects were randomly assigned to placebo, ketoconazole (to inhibit T synthesis) at 400 or 800 mg, dutasteride (to inhibit T metabolism) 2.5 mg, or anastrazole (to inhibit T metabolism) 1 mg, daily for 7 days (n = 8/group). Intratesticular steroid concentrations were measured 48 hours after acyline administration alone and again after 7 days of combination treatment. After 7 days of combination treatment, the median IT-T (25th, 75th percentile) in the placebo group was 14 (8.0, 21.2) ng/mL. IT-T was reduced to 3.7 (2.5, 7.1) ng/mL in the ketoconazole 400 mg group and 1.7 (0.8, 4.0) ng/mL in the ketoconazole 800 mg group (P < .001 vs placebo for both comparisons). IT-T concentrations in the dutasteride and anastrazole groups were similar to placebo. Combining inhibition of steroidogenesis with gonadotropin suppression lowers IT-T more than gonadotropin suppression alone. This combination might be useful to determine the minimum IT-T concentration necessary for human spermatogenesis, information essential for developing male hormonal contraceptives. PubMed Abstract Full text: PMC3590466

Roth MY et al; J Clin Endocrinol Metab. 2013 Mar;98(3):1198-206 (2013)

from HSDB

/SURVEILLANCE/ /The purpose of this study was /to evaluate the incidence of Ketoconazole associated hepatotoxicity and related factor. Literature retrieval was conducted by using multi-databases for meta-analysis on Ketoconazole associated hepatotoxicity. The data were collected with a standardized form. Overall estimation of incidence of hepatotoxicity for specific study type was calculated by using a DerSimonian-Laird random-effects model owing to the substantial differences among the studies. Totally 204 eligible studies were included in the analysis. The incidence of Ketoconazole associated hepatotoxicity was 3.6%-4.2%. The dosage and duration specific subgroup analyses did not show any significant difference among groups, while the age specific subgroup analysis showed the incidence in children and people aged >60 years was 1.4% (95% CI: 0.5%-4.2%) and 3.2% (95% CI: 1.1%-8.7%) respectively. Additionally, the incidence of the hepatotoxicity was higher in people who had oral administration of ketoconazole beyond the provisions of the usage instructions, and the incidence was 5.7% (95% CI: 4.5%-7.2%). Ketoconazole associated hepatotoxicity was common. Off-label use might increase the risk of liver damage. ... PubMed Abstract

Yan JY et al; Biomed Environ Sci 26 (7): 605-10 (2013)

from HSDB

/ENDOCRINE MODULATION/ Usual dosages (ie, 200-400 mg daily) of ketoconazole have been reported to transiently (for 2-12 hours) inhibit testicular testosterone synthesis. A compensatory increase in serum luteinizing hormone (LH) concentrations may occur.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

/ENDOCRINE MODULATION/ Further study is needed to fully elucidate the effects of ketoconazole on steroid synthesis in humans, but the drug apparently directly inhibits synthesis of adrenal steroids and testosterone in vitro and in vivo. Ketoconazole appears to inhibit steroid synthesis principally by blocking several P-450 enzyme systems (eg, 11beta-hydroxylase, C-17,20-lyase, cholesterol side-chain cleavage enzyme).

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

from HSDB

/ENDOCRINE MODULATION/ Widely used conazole antifungals were tested for endocrine disruptive effects using a panel of in vitro assays. They all showed endocrine disrupting potential and ability to act via several different mechanisms. Overall the imidazoles (econazole, ketoconazole, miconazole, prochloraz) were more potent than the triazoles (epoxiconazole, propiconazole, tebuconazole). The critical mechanism seems to be disturbance of steroid biosynthesis. In the H295R cell assay, the conazoles decreased the formation of estradiol and testosterone, and increased the concentration of progesterone, indicating inhibition of enzymes involved in the conversion of progesterone to testosterone. Prochloraz was most potent followed by econazole~miconazole>ketoconazole>tebuconazole>epoxiconazole>propiconazole. In the MCF-7 cell proliferation assay, the conazoles showed anti-estrogenic effect, including aromatase inhibition, since they inhibited the response induced by both 17beta-estradiol (miconazole>econazole~ketoconazole>prochloraz>tebuconazole>epoxiconazole>propiconazole) and testosterone (econazole>miconazole>prochloraz>ketoconazole>tebuconazole>epoxiconazole>propiconazole). The triazoles were anti-androgenic in an androgen receptor reporter gene assay (epoxiconazole~tebuconazole>propiconazole). This effect could not be evaluated for the pharmaceutical imidazoles due to cytotoxicity. PubMed Abstract

Kjaerstad MB et al; Reprod Toxicol 30 (4): 573-82 (201)

from HSDB

12.1.12 Non-Human Toxicity Excerpts

/LABORATORY ANIMALS: Acute Exposure/ After oral administration toxicity was manifested in mice, rats and guinea pigs by sedation, catalepsy, ataxia, tremors, convulsions and pre-lethal loss of the righting reflex at doses >320 mg/kg. In dogs, toxicity was manifested by diarrhea and vomiting at doses >80 mg/kg.

Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p24 (Revision date: March 4, 2014). Available from, as of November 12, 2014: ***http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

/LABORATORY ANIMALS: Acute Exposure/ Ketoconazole has been administered by the oral (gavage) and intravenous routes to mice, rats, guinea pigs and dogs. Toxicity after intravenous administration was manifested by spasms, convulsions and dyspnea in rats, mice and guinea pigs; pre-lethal loss of the righting reflex occurred in mice and guinea pigs, and dogs. Toxicity in dogs was also manifested by licking and convulsions.

Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p24 (Revision date: March 4, 2014). Available from, as of November 12, 2014: ***http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Four groups of 10 male and 10 female rats were dosed orally for a period of 13 weeks with 0, 10, 40 and 160 mg/kg/day ketoconazole added to the diet. Hematology was normal in all groups. No deleterious effects on serum analyses were seen in males at 10 and 40 mg/kg. At 160 mg/kg **potassium** and BUN decreased significantly. In female rats dosed at 10 mg/kg no relevant differences in serum analyses were found between control and treated animals. At 40 and 160 mg/kg serum **sodium** increased significantly, while BUN and **potassium** decreased. A decrease in **chloride** and increase in alkaline phosphatase at 160 mg/kg are also considered to be among the drug and dose-related effects. In control, low and medium dosed males and females and in the high-dosed males no abnormalities were seen in urinalyses. At 160 mg/kg, female rats had increased excretion of urine and decreased **creatinine**. In 3 of 10 females, casts were seen at the high dose. In animals of both sexes dosed with 10 mg/kg and in male rats dosed at 40 mg/kg, ketoconazole had no effect on mortality, behaviour, appearance, food consumption, body weight, gross pathology, organ weight, or histology. Female rats dosed at 40 mg/kg were not significantly different from undosed female rats with respect to mortality, behaviour, appearance, food consumption or body weight. However, at 40 mg/kg discolored livers were seen in 5/10 female rats, pale adrenals in 5/10 and slightly larger ovaries in 8/10. Marginal increases were seen in the absolute and relative weight of the liver and ovaries. Histologically the livers of the female rats dosed at 40 mg/kg appeared normal. In the adrenals the following changes were noted: a glomerulosa zone devoid of fat, and a fatty overload in the fasciculata and reticularis zones. The disturbed aspect of the inner zone was a result of increased RE framework, swelling of pigment-loaded sinusoidal cells and macrophage activity. A clearer aspect of the interstitial tissue of the ovary was also noted at histology. One female dosed at 40 mg/kg exhibited swelling of the convoluted tubule and/or loop of Henle in the kidney. At 160 mg/kg, 2 male rats died whereas all females survived. Behaviour and appearance was normal in males whereas swollen eyelids were seen in all high-dosed females with some exhibiting this as early as after 2 months of dosing. Fragile leg bones were noted in 9/10 female rats with 4/10 having broken legs. Total food consumption decreased significantly in both sexes as did total weight gain and terminal body weight. These phenomena appeared during the first week of dosing. Gross pathology also revealed the following changes: discolored livers 6/10 males, 9/10 females; pale adrenals 1/10 male, 9/10 females; pseudopregnancy 9/10 females. Relative weight increase of liver and adrenals, and increases in the relative and absolute weights of the testes were noted in high-dosed male rats. Female rats exhibited increased absolute and relative weight of liver and adrenals as well as increase in the relative weight of spleen and kidney. Histology indicated the following drug induced changes: slight centrilobular swelling and/or finely granular or blurred aspect of the cytoplasm of the liver with brown hepatocytic pigmentation; swelling of the distal tubules and/or loops of Henle in the kidney; the uterus was small and exhibited an anoestral aspect, the vaginal epithelium was mucified or thin; the ovary was characterized by an increased amount of interstitial glandular tissue with large clear cells, highly vacuolated corpora lutea and conspicuous follicular cysts which were sometimes atretic and leading to interstitial tissue formation; in both sexes the adrenals were characterized by a thin glomerulosa zone devoid of fat, fatty overload in the fasciculata and especially in the reticularis zones with macrophage activity, RE stimulation and eventually infiltration with round cells. The weakness of the bony tissues seen in the high dosed females was manifested on histological examination by diminished diameter of the tibial bone, and irregularities in the mineralization of the compact bone; cancellous bone hyperplasia and spontaneous fractures which were the sites of callus formation with marked fibrosis eventually extending far into the neighboring tissues.

Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p25-7 (Revision date: March 4, 2014). Available from, as of November 12, 2014: ***http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ In the Wistar rat (200 males, 200 females), oral administration of 0,5, 20 and 80 mg/kg/day of ketoconazole in the diet for 24 months did not affect the mortality rate as compared to controls. At necropsy the following dose-related effects were seen: a brownish aspect of the salivary glands and the abdominal fat in medium and high-dosed animals and broken legs in one high-dosed male, 2 medium-dosed females and 10 high-dosed females. These findings have been identified in the 18 month rat toxicity study. The overall incidence of and type of tumors was not significantly different between treated and control groups, except for high-dosed female rats who had a decrease of the overall tumor rate.

Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p32 (Revision date: March 4, 2014). Available from, as of November 12, 2014: ***http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ Four groups of 50 male and 50 female albino Swiss mice received doses of 0, 5, 20 and 80 mg/kg/day of ketoconazole administered via the diet for 18 months. There were no significant differences between groups on overall mortality or on the time of death. There were no statistically significant differences between groups in the incidence or type of tumors. In a small number of dosed male mice (4-6%) decreased size

of testes and mammary stimulation were seen at necropsy. An increased incidence of brownish aspect of the salivary glands was also noted in animals of both sexes dosed with 80 mg/kg/day. The most significant finding was a dose related increase in pathology of the pancreas (brownish aspect) which was not seen in control animals but occurred in approximately 50% of high-dosed males and females.

Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p31-2 (Revision date: March 4, 2014). Available from, as of November 12, 2014: ***http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

from HSDB

/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ ovaries, adrenals and prostate gland. In the liver, lipo-pigment also accumulated in the hepatocytes. Interstitial parotitis with reduced zymogen storage was seen in one dog. No spermatogenic activity was noted in 2/3 dogs - one having an immature aspect and the other a degenerated germinal epithelium. Lipofuscin loaded Leydig cells were noted in 2/3 dogs. An increase of clear replacement cells and reduced amount of secretion of the prostate was noted in the dogs with no spermatogenic activity.

Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p31 (Revision date: March 4, 2014). Available from, as of November 12, 2014: ***http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

from HSDB

/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ Three male and 3 female Beagle dogs were orally dosed with gelatin capsules containing increasing doses of ketoconazole (20, 40, 60 mg/kg/day) for a period of 6 months. One animal (60 mg/kg) died of gastroenteritis and nephritis during week 12. A dose-related body weight loss was seen above 20 mg/kg/day coincident with reduced appetite. There was no effect on the ECG at any dose and serum analyses and haematology were normal during the 20 and 40 mg/kg dosage periods. At 60 mg/kg/day an increase in SGOT and haptoglobin, a slight decrease of total protein and albumin and a pronounced increase of alkaline phosphatase and SGPT were seen. Decreases of haematocrit, haemoglobin and RBC were seen in most animals during the 60 mg/kg dosage period. Both serum analyses and haematology normalized during the withdrawal period. Gross pathology revealed a small sized thymus (decreased absolute and relative weight) and swollen liver (increased relative and absolute weight) at 60 mg/kg; however, these effects were reversible since they normalized during the withdrawal period. Histology indicated the presence of macrophages loaded with lipofuscin in the gallbladder, liver, ileum, spleen, lymph nodes, testes, ovaries, adrenals and prostate gland. In the liver, lipo-pigment also accumulated in the hepatocytes. Interstitial parotitis with reduced zymogen storage was seen in one dog. No spermatogenic activity was noted in 2/3 dogs - one having an immature aspect and the other a degenerated germinal epithelium. Lipofuscin loaded Leydig cells were noted in 2/3 dogs. An increase of clear replacement cells and reduced amount of secretion of the prostate was noted in the dogs with no spermatogenic activity.

Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p30-1 (Revision date: March 4, 2014). Available from, as of November 12, 2014: ***http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

from HSDB

/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ Four groups of 3 male and 3 female Beagle dogs received ketoconazole for 12 months at 0, 2.5, 10 and 40 mg/kg/day administered in gelatin capsules. Behavior was normal in the 0, 2.5 and 10 mg/kg/day groups; however, at 40 mg/kg decreased appetite and sporadic emesis were noted in all animals during the entire study. No drug-related mortality was observed; however, body weight gain was significantly lower in the high-dose group during the entire experimental period. Heart rate, blood pressure and ECG were normal throughout the experiment. Hematology parameters were unchanged except in the high-dose group, where a marginally low hemoglobin value was noted during the entire dosing period. Urinalyses and serum analyses were normal except in the high-dose group, where a marginal decrease of albumin from week 24 onwards and persistently high alkaline phosphatase and SGPT values during the entire dosing period were noted. Gross pathology was normal in all groups except the high-dose group, where all dogs exhibited dark colored livers, brownish discolored pancreas, thymus, adrenals, thyroid, testes, ovaries, lymph nodes and fatty tissue and gray colored ovaries. In the high-dosed group, the absolute weight of several organs decreased with an increase of the relative organ weight. Absolute and relative liver weight increased in the high-dose group. Histology revealed deposition and marked accumulation of a granular yellowish pigment in macrophages in various tissues (in the ovaries, in the hepatocytes, in the fasciculata and glomerulosa zones of the adrenals, in the biliary epithelium and in the interstitial tissue and Leydig cells of the testis) in a dose-related fashion at 10 and 40 mg/kg/day. The livers of the 40 mg/kg dosed males were devoid of **glycogen**. Large vacuolated cells were seen in the fasciculata zone of the adrenals of the high-dosed animals of both sexes. Desquamation and spermatid giant cells were conspicuous in some 40 mg/kg dosed dogs and one dog showed reduced spermatogenic activity. Many macrophages with yellowish pigment were seen in the 40 mg/kg dosed dogs and in 2/3 female dogs dosed at 10 mg/kg.

Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p29-30 (Revision date: March 4, 2014). Available from, as of November 12, 2014: ***http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

from HSDB

/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ Four groups of 20 male and 20 female adult Wistar rats received 0, 5, 20 and 80 mg/kg/day ketoconazole through the diet for 18 months. Mortality tended to increase with increasing doses in both sexes; however, these increases were not statistically different from controls except for female mortality at 80 mg/kg/day (15/20 high-dose vs. 7/20 control group). Body weight gain and final body weight were lower in the mid-dosed females and in both the high-dosed males and females. Marginal increases in hemotocrit and hemoglobin were seen in high-dosed females. Other serum analyses and urinalysis values were considered normal except for a decrease in serum **potassium** in the high-dosed males. Gross pathology revealed the following changes: brownish aspect of the salivary glands and the abdominal fat in some mid-dosed and several high-dosed animals; swollen adrenals in 3/16 high-dosed males, 4/20 middosed females and 2/20 high dosed females; bone fragility in the legs leading to broken legs (control-l, low-dose-5, medium-2, high-6). At 80 mg/kg/day, relative organ weights in both sexes increased. This correlated with a decrease in final body weight. Absolute organ weights were normal in all groups except for an increase in adrenal

weights in both males and females. The following histological changes were noted: increased deposition and accumulation of lipogenic pigment in some parenchymal and lymphoid tissues (heart, tongue, liver, spleen, lymph nodes, adrenals); ovaries of the mid and high-dosed females showed an increased number of old corpora lutea, and an increased deposition of yellowish to brown pigment in the interstitial cells; the adrenals of the low-dosed females and the mid and high-dosed males and females showed an increased vacuolization of the fasciculata and the reticularis zones and a diminished size of the glomerulosa zone. In the rat, ketoconazole shows an affinity for the liver and adrenal glands of both sexes and for the sex organs of the female. Ketoconazole is associated with significant bone fragility which is more pronounced in female than in male rats. In the rats from the 6, 12 and 18 month oral diet toxicity studies, radiometry and direct photon absorptiometry were applied to assess the significance of the observed increase in bone fragility. The results indicate a dose-related decrease of cortical bone area which is present in both sexes at 40 and 80 mg/kg and to a lesser extent in females dosed at 20 mg/kg. Bone mineral content per unit of width however was unaffected, demonstrating the absence of osteoporosis. The mechanism for this condition remains unclear - the induction of menopause in female rats could be a contributing factor.

Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p27-8 (Revision date: March 4, 2014). Available from, as of November 12, 2014: ***http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ Four groups of 20 male and 20 female adult Wistar rats received ketoconazole at oral doses of 0, 5, 20 and 80 mg/kg/day added to the diet for a period of 6 months. No adverse effects were seen at the 5 mg/kg dose. One control male and 2 high-dosed females died during the course of the study. Food consumption and body weight were significantly decreased in high dosed males and mid-dosed and high-dosed females. A significant increase in lymphocytes and decrease in segmented heterophils was seen in the mid-dosed and high-dosed males, as well as a significant decrease in serum **potassium** in mid and high-dosed females. Urinalyses were normal except for the presence of casts in several high-dosed males (11/20) and females (7/20) and in some of the mid-dosed females (4/20). Gross pathology was normal except for broken legs in 1/20 mid and 6/20 high-dosed females. Organ weights were normal except for a significant increase in liver weight seen in high-dosed males and females and a significant increase in the weights of the kidneys and brain in the highdosed females. Histology showed fatty surcharge of the ovary and adrenals in the mid and high-dosed groups. The ovaries showed a tendency to more vacuolation of the corpora lutea and an increase in lipofuscin. In the adrenals there was fatty surcharge of the fasciculata and reticularis zones, lipofuscin formation and macrophagy. Finally an interstitial fibrotic reaction was noted near the medulla in rats of both sexes dosed at 80 mg/kg and in mid-dosed females.

Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p27 (Revision date: March 4, 2014). Available from, as of November 12, 2014: ***http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ In a ... rat study, ketoconazole was administered by gavage from day 6 through 15 of pregnancy at doses of 0, 10, 40 and 160 mg/kg body weight. Twenty dosed females were used per dosage group. This study was designed to compare the effects of administering the test substance through the diet at comparable dose levels. Foetuses were delivered by caesarean section on Day 22 of presumed pregnancy. At doses of 10 and 40 mg/kg, no evidence of maternal toxicity was observed except for an increase in the number of resorptions at 40 mg/kg from 1.2% (control) to 3.6%. There was a doserelated increase in the incidence of oligodactyly in fetuses delivered from the females of this experiment. At 160 mg/kg, 19 of 20 dosed females died between the 3rd and 6th day of drug administration. No pregnancy occurred in the surviving female.

Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p34-5 (Revision date: March 4, 2014). Available from, as of November 12, 2014: ***http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ In a fourth rat study, ketoconazole was administered by gavage from day 6 through 15 of pregnancy, at doses of 0, 2.5, 10 and 40 mg/kg body weight. Twenty dosed females were used per dosage group. This study was designed to determine whether the bone missing in the fetuses of Study 3 were actually missing or not yet ossified. Female rats were allowed to deliver their fetuses normally. The results of this experiment indicate that metacarpal and metatarsal bones were not really missing but were ossified when females were allowed to deliver their fetuses normally. However, the incidence of stillborn fetuses increased from a control value of 0.5% to 32.7% in rats dosed with 40 mg/kg and cannibalization of young occurred in two litters.

Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p35 (Revision date: March 4, 2014). Available from, as of November 12, 2014: ***http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ Administration of ketoconazole, an **imidazole** antifungal agent (400 mg/kg b.wt. orally for a period of 60 days) resulted in a significant decline in sperm motility and density in cauda epididymis. A sharp decline in fertility (50% negative) in ketoconazole treated mice was observed. A significant reduction in the total protein and sialic acid contents of testes, epididymis, seminal vesicle and ventral prostate were noticed. The **cholesterol** contents of testes were raised while **fructose** contents of seminal vesicle were reduced significantly. The ketoconazole treatment altered the biochemical milieu of the reproductive tract. The mechanism of action is discussed.
PubMed Abstract

Joshi SC et al; Acta Eur Fertil 25 (1): 55-8 (1994)

▸ from HSDB

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ Two studies were done in Wistar rats. In the first study, ketoconazole was administered through the diet at doses of 0, 10, 40 and 160 mg/100 g food and, in the second study,

ketoconazole was given by gavage at doses of 0, 10, 40 and 80 mg/kg body weight. Ketoconazole was administered from day 16 of pregnancy through a 3 week lactation period. Twenty females per dosage group were used or, in total, 160 females. Again, both studies were designed to compare the effects of the administration of ketoconazole through the diet and by gavage. When administered through the diet at a dose of 10 mg/100 g food, no effects could be observed on body weight, food consumption, mortality, pregnancy rate and duration of gestation. Also, no effects were observed on litter size, weight of pups at birth and at 3 weeks of age, and survival rate during a 3 week observation period. At 40 mg/100 g food, the only evidence of maternal toxicity was a slight decrease (approximately 12%) of food consumption. At 40 mg/100 g food, there was a 15% reduction in the number of live fetuses and a similar decrease in the survival rate of the pups was seen at 3 weeks indicating that ketoconazole is embryotoxic at 40 mg/100 g food. No abnormalities were recorded in the litters; however, at 40 mg/kg, cannibalism by the mother occurred in 2 litters. At a dose of 160 mg/kg maternal toxicity was indicated by a 10% mortality, lower weight gain (1/10th of control), lower food consumption (approximately 30% reduction) and a slightly decreased pregnancy rate (20% reduction). Embryotoxicity was indicated by an increase (approximately 10%) in the percentage of stillborn fetuses. This figure is possibly low due to an increase in cannibalization of foetuses (37% of litters). Birth weight was lower and most pups died shortly after birth. Surviving pups showed no weight increase after a 3-week period. When ketoconazole is administered by gavage to pregnant rats, maternal and embryotoxicity occur in a dose-dependent manner. At 10 mg/kg, the average weight gain of the dams is reduced by 15% although food consumption is minimally affected. At this same dose the percentage of still born fetuses increased to 3.4% as compared to <1% in control animals and mean litter size decreased from 12.4 in controls to 10.4 in rats dosed at 10 mg/kg. At 40 mg/kg and 80 mg/kg, maternal toxicity was manifested by increased mortality (25 and 90%, respectively). Furthermore at 40 mg/kg, 50% of the fetuses were stillborn and the remainder died shortly after birth. At 80 mg/kg, no live fetuses were born. In animal studies, the toxicity of ketoconazole was manifested at lower doses when ketoconazole was administered by gavage as opposed to being admixed in the diet.

Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p36-7 (Revision date: March 4, 2014). Available from, as of November 12, 2014: ***http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ In a rabbit study, ketoconazole was administered by gavage from day 6 through 18 of pregnancy at doses of 0, 10, 40 mg/kg body weight. Twenty dosed females were used per dosage group. The rabbits were artificially inseminated and fetuses were delivered by caesarean section on day 28 after the dam was inseminated. Survival rate was 100% for the control and 10 mg/kg groups. Two females dosed at 40 mg/kg died. The number of resorptions was increased significantly in a dose-dependent manner from 8.1% in control animals to 21.2% and 27.2% in animals dosed at 10 and 40 mg/kg, respectively. Bone deformities were seen in foetuses born to both control and treated animals although at 40 mg/kg their incidence was increased. One foetus born to a control animal had exencephaly and one born to the high dosage group was small sized and had coelosomy. In the rabbit, ketoconazole produces evidence of maternal toxicity, embryotoxicity and teratogenicity at a high dose of 40 mg/kg/day.

Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p35 (Revision date: March 4, 2014). Available from, as of November 12, 2014: ***http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ In two rat studies, ketoconazole was administered through the diet from day 6 through day 15 of pregnancy at doses of respectively, 0, 10, 40, and 160 mg/100 g food and at 0, 10, 20, 40, 80 and 160 mg/100 g food. Twenty dosed females were used per dosage group, or, in total, 80 and 120 females for the two studies respectively. In both studies, the body weight gain of the dosed pregnant rats was normal and comparable between groups, except for a possible slight decrease in food consumption apparent in some groups, i.e. 160 mg/100 g food of the first study, and 40 and 80, but not 160 mg/100 g food of the second study, so that no dose-related effect on food consumption was apparent. No mortalities occurred in any group and pregnancy rate was normal in all groups except for the 160 mg/100 g food dosed groups, where the pregnancy rate decreased by approximately 50%. No embryotoxic effects were seen in the 10, 20, 40 and 80 mg/100 g food dosed groups, whereas at 160 mg/100 g food, litter size and weight of pups at delivery decreased. The number of resorptions increased from <2% in control animals to >17.7% and >30% in the high dosed animals of the two studies. These results indicate a definite embryotoxic effect at the 160 mg/100 g food dose. In rats of both studies dosed at 10, 20 and 40 mg/100 g food, the type (waved ribs, absence of metacarpal and/or metatarsal bones) and incidence of abnormalities was the same as that seen in the undosed control rats except for one female of the second study dosed at 20 mg/100 g who delivered 2 foetuses showing retarded embryological development. At 80 and 160 mg/100 g food a clear teratogenic effect was seen with >70% of the foetuses in both studies having abnormalities which included oligodactylia or syndactylia as well as the aforementioned abnormalities. Coelosomia was also seen in one foetus at 160 mg/kg.

Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p33-4 (Revision date: March 4, 2014). Available from, as of November 12, 2014: ***http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ Wistar rats received ketoconazole administered through the diet at doses of 0, 10, 20, 40 and 80 mg/100 g food. Twenty dosed males coupled each with a non-dosed female and 20 non-dosed males coupled each with a dosed female were used per group or, in total, 200 males and 200 females. Animals were sacrificed on the 22nd day of pregnancy and the fetuses were delivered by caesarean section. In the various groups of non-dosed females, no effects could be observed on body weight, food consumption, pregnancy rate and duration of gestation of the adult females. One female mated with a male dosed at 40 mg, died during the study. No effects were observed on the number of implantations, litter size, weight of pups at delivery, number and distribution of live, dead and resorbed fetuses. No teratogenic effects were seen. In the various groups of females dosed at 10, 20 and 40 mg/100 g food, no effects could be observed on any of the parameters studied. The incidence and type of abnormalities seen in the litters of animals dosed at 10 and 20 mg/100 g food were similar to those in the litters of control animals (waved ribs and the absence of one or more metatarsal or metacarpal bones). At 40 mg/100 g food, abnormal knee formation and hydrops of the hind quarters also observed. The duration of gestation of the pregnant females in this group was normal, however,

embryotoxicity was manifested by a decrease in the number of implantation sites, a decrease in litter size, a decreased weight of pups at delivery and an increased resorption rate. One female dosed at 80 mg/100 g food died. At 80 mg/100 g food, dosed females showed a lower body weight gain and a lower food intake with a decreased pregnancy rate which are indicative of maternal toxicity. At 80 mg/100 g food, a clear teratogenic effect was observed and included syndactyly, oligodactyly as well as abnormal head and leg formation.

*Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p32-3 (Revision date: March 4, 2014). Available from, as of November 12, 2014: **http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

▸ from HSDB

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ In order to investigate the morphological effects of ketoconazole on hypertrophied placentas, we examined the sequential histopathological changes in the placenta from rats exposed to ketoconazole. Ketoconazole was administered orally at 0 and 25 mg/kg/day during gestation days (GDs) 12 to 14, and the placentas were sampled on GDs 15, 17 and 21. All dams showed neither effect on body weight nor any abnormal clinical signs during the experimental period. In the treated group, the placentas appeared more hypertrophic with increases in the weight, diameter and thickness on GD 21. Histopathologically, increased thickness was noted in the labyrinth zone and basal zone on GDs 17 and 21, while on GD 15 the change had been already evident in the former zone. In the labyrinth zone, the mitotic figures of the trophoblasts were significantly elevated on GD 15. A multiple cystic dilatation of maternal sinusoids was observed in some placentas on GDs 15, 17 and 21. In the basal zone, an increase in spongiotrophoblasts and clusters of **glycogen** cells were detected on GDs 17 and 21. In the decidua basalis, there were no significant changes in either histology or thickness between the control and treated group during GDs 15 to 21. In conclusion, ketoconazole increased the population of composed cells in the labyrinth and basal zone, leading to placental hypertrophy in pregnant rats. **PubMed Abstract**

Furukawa S et al; J Vet Med Sci 70 (11): 1179-84 (2008)

▸ from HSDB

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ The effect of ketoconazole on the fertility of male rats was evaluated. Three days of oral dosing with ketoconazole at 200 mg/kg reduced fertility compared to controls. A complete loss of fertility was observed after doses of 400 mg/kg. There was no change in the testicular weight, epididymal sperm concentration or epididymal weight between the control and treatment groups. Motility was reduced in the high-dose group and forward progression was reduced in both dosing groups compared to control. These data support previous observations in the dog and primate that orally administered ketoconazole alters sperm viability. ... **PubMed Abstract**

Waller DP et al; Contraception 41 (4): 411-7 (1990)

▸ from HSDB

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ Skeletal changes induced by treatment of pregnant rats with four potent teratogens, **busulfan**, **acetazolamide**, **vitamin A palmitate**, and ketoconazole, were evaluated using **Alizarin Red S** and **Alcian Blue** double-staining to investigate the relationship between drug-induced skeletal malformations and cartilaginous changes in the fetuses. Pregnant rats (N = 8/group) were treated once or twice between gestation days (GDs) 10 to 13 with **busulfan** at doses of 3, 10, or 30 mg/kg; **acetazolamide** at 200, 400, or 800 mg/kg; **vitamin A palmitate** at 100,000, 300,000, or 1,000,000 IU/kg; or ketoconazole at doses of 10, 30, or 100 mg/kg. Uterine evaluations and fetal external and skeletal examinations were conducted on GD 20. Marked skeletal abnormalities in ribs and hand/forelimb bones such as absent/ short/bent ribs, fused rib cartilage, absent/fused forepaw phalanx, and misshapen carpal bones were induced at the mid- and high-doses of **busulfan** and **acetazolamide** and at the high-dose of **vitamin A palmitate** and ketoconazole. Increased incidences of discontinuous rib cartilage (DRC) and fused carpal bone (FCB) were observed from the low- or mid-dose in the **busulfan** and **acetazolamide** groups, and incidences of FCB were increased from the mid-dose in the **vitamin A palmitate** and ketoconazole groups. Therefore, DRC and FCB were detected at lower doses than those at which ribs and hand/forelimb malformations were observed in the four potent teratogens. **PubMed Abstract**

Dodo T et al; Hum Exp Toxicol 29 (6): 439-50 (2010)

▸ from HSDB

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ Ketoconazole is an **imidazole** antifungal agent that is known to inhibit C17,20-lyase and aromatase activity in the mammalian steroid biosynthesis pathway, resulting in a decline in the production of androgen and estrogen. In rats, deficiency of these hormones following ovariectomy at mid-gestation is known to induce excessive placental hypertrophy, indicating that placental growth is closely related to maternal ovarian function. In this study, therefore, we have investigated the effects of ketoconazole on placental weights associated with maternal plasma **estradiol** levels. Ketoconazole was administered orally at a dosage level of 25 mg/kg/day to pregnant Crl:CD(SD) rats on gestation days (GD) 9-11, 12-14 or 15-17 and the placental weight on GD20 was evaluated. The plasma estradiol 17beta levels were also measured on the last day of dosing for the GD1-14- and GD15-17-treated groups. The placental weights were significantly increased in GD1-14- and GD15-17-treated groups and the plasma **estradiol-17beta** level declined significantly in the GD12-14-treated group. In order to examine the effects of **estradiol-17alpha** supplement on ketoconazole-induced placental hypertrophy, **estradiol-17beta** at dosage levels of 0.1 and 1 g/rat/day was administered subcutaneously on GD12-14 using an osmotic pump in combination with 25 mg/kg/day ketoconazole treatment. At necropsy on GD20, the placental weights in the **estradiol-17beta** co-administered group were significantly lower than in the ketoconazole-treated group. From these results, it is indicated that ketoconazole induces an increase in placental weights and this is considered to be caused by reduced maternal plasma **estradiol** levels.

Ichikawa A et al; Congenit Anom (Kyoto) 46 (4): A23 (2006)

▸ from HSDB

/ENDOCRINE MODULATION/ We performed a 28-day repeated-dose toxicity study of ketoconazole, a widely used an antimycotic drug ... to investigate whether ketoconazole has endocrine-mediated properties ... . Seven-week-old SD rats were administered with ketoconazole daily by oral gavage at doses of 0, 6.25, 25 or 100 mg kg(-1) day(-1) for at least 28

days. The ketoconazole-treated male rats showed reduction of epididymis and accessory sex organ weights, spermatid retention in the seminiferous tubules, decrease of **testosterone** and increases of **estradiol**, luteinizing hormone (LH) and follicular stimulating hormone (FSH). A prolongation of the estrous cycle and increases of **estradiol**, LH and FSH were observed in the treated female rats. **Thyroxin** and **triiodothyronine** were decreased and thyroid-stimulating hormone was increased in both sexes; however, there were no compound-related microscopic lesions in the thyroid gland or changes in the thyroid weight. The endocrine-related effects of ketoconazole could be detected by the parameters examined in the present study ... . **PubMed Abstract**

Shin JH et al; Arch Toxicol 80 (12): 797-803 (2006)

▸ **from HSDB**

/ENDOCRINE MODULATION/ The endocrine-disrupting potential of four commonly used **azole** fungicides, **propiconazole**, **tebuconazole**, **epoxiconazole** and ketoconazole, were tested in two short-term in vivo studies. Initially, the antiandrogenic effects of **propiconazole** and **tebuconazole** (50, 100 and 150 mg/kg body weight/day each) were examined in the Hershberger assay. In the second study, pregnant Wistar rats were dosed with **propiconazole**, **tebuconazole**, **epoxiconazole** or ketoconazole (50 mg/kg/day each) from gestational day (GD) 7 to GD 21. Caesarian sections were performed on dams at GD 21. **Tebuconazole** and **propiconazole** demonstrated no antiandrogenic effects at doses between 50 and 150 mg/kg body weight/day in the Hershberger assay. In the in utero exposure toxicity study, ketoconazole, a pharmaceutical to treat human fungal infections, decreased anogenital distance and reduced testicular **testosterone** levels, demonstrating a demasculinizing effect on male fetuses. **Tebuconazole**, **epoxiconazole** and ketoconazole induced a high-frequency of post-implantation loss, and both ketoconazole and **epoxiconazole** caused a marked increase in late and very late resorptions. Overall the results show that many of the commonly used **azole** fungicides act as endocrine disruptors in vivo, although the profile of action in vivo varies. As ketoconazole is known to implicate numerous endocrine-disrupting effects in humans, the concern for the effects of the other tested **azole** fungicides in humans is growing. **PubMed Abstract**

Taxvig C et al; Int J Androl. 2008 Apr;31(2):170-7 (2008)

▸ **from HSDB**

/ENDOCRINE MODULATION/ This study evaluated changes in the expression of steroidogenesis-related genes in male fathead minnows exposed to ketoconazole (KTC) or **vinclozolin** (VZ) for 21 days. The aim was to evaluate links between molecular changes and higher level outcomes after exposure to endocrine-active chemicals (**EACs**) with different modes of action. To aid our analysis and interpretation of EAC-related effects, we first examined variation in the relative abundance of steroidogenesis-related gene transcripts in the gonads of male and female fathead minnows as a function of age, gonad development, and spawning status, independent of EAC exposure. Gonadal expression of several genes varied with age and/or gonadal somatic index in either males or females. However, with the exception of aromatase, steroidogenesis-related gene expression did not vary with spawning status. Following the baseline experiments, expression of the selected genes in male fathead minnows exposed to KTC or VZ was evaluated in the context of effects observed at higher levels of organization. Exposure to KTC elicited changes in gene transcription that were consistent with an apparent compensatory response to the chemical's anticipated direct inhibition of steroidogenic enzyme activity. Exposure to VZ, an antiandrogen expected to indirectly impact steroidogenesis, increased pituitary expression of follicle-stimulating hormone beta-subunit as well as testis expression of 20beta-hydroxysteroid dehydrogenase and luteinizing hormone receptor transcripts. Results of this study contribute to ongoing research aimed at understanding responses of the teleost hypothalamic-pituitary-gonadal axis to different types of **EACs** and how changes in molecular endpoints translate into apical outcomes reflective of either adverse effect or compensation. **PubMed Abstract**

Villeneuve DL et al; Toxicol Sci 98 (2): 395-407 (2007)

▸ **from HSDB**

/ENDOCRINE MODULATION/ Effects of two model **imidazole**-type fungicides, **prochloraz** (PCZ) and ketoconazole (KTC), on the hypothalamic-pituitary-gonadal (HPG) axis of the Japanese medaka (Oryzias latipe) [corrected] were examined by use of real time PCR (RT-PCR) array. Fourteen-week-old Japanese medaka were exposed for seven days to concentrations of PCZ or KTC from 3.0 to 300 microg/L Exposure [corrected] to KTC or PCZ caused significant reduction of fecundity of Japanese medaka and down-regulated expression of estrogen receptor (ER)-alpha and egg precursors in livers of males and females. However, PCZ was more potent than KTC both in modulating transcription and causing lesser fecundity. Exposure to nominal 30 microg PCZ/L resulted in 50% less fecundity and significant down-regulation of vitellogenin II expression, but KTC did not cause such effects at this concentration. Exposure to PCZ caused a compensatory upregulation in cytochrome P450 c17alphahydroxylase, 17,20-lyase (CYP17) and aromatase (CYP19) expression in the ovary, while KTC did not. Furthermore, the ecologically relevant end point, fecundity was log-log related to mRNA level of six genes in livers of females. **PubMed Abstract**

Zhang X et al; Environ Sci Technol 42 (17): 6762-9 (2008)

▸ **from HSDB**

/GENOTOXICITY/ Ketoconazole did not show any signs of mutagenic potential when evaluated using the dominant lethal mutation test or the Ames Salmonella microsomal activator assay.

American Society of Health-System Pharmacists 2014; Drug Information 2014. Bethesda, MD. 2014

▸ **from HSDB**

/ALTERNATIVE and IN VITRO TESTS/ In this study we have compared the effects of ketoconazole and **fluconazole**, a novel triazole antifungal agent, on **17-beta estradiol** production in rat ovaries in vitro. For both compounds there was a lag phase, immediately after addition to the test system, during which the rate of **oestradiol** synthesis remained at control values. This may have been due to the time required for uptake of the compound and transfer to its site of action or for depletion of endogenous pools of intermediates. After the lag phase both compounds produced a reduction in the rate of **estradiol** synthesis. At any given concentration, **fluconazole** produced a reduction which was substantially less than that observed with ketoconazole. Indeed 2 microM ketoconazole reduced the rate of **oestradiol** production by greater than 90% while 10 microM **fluconazole** caused only a 70% reduction. These findings are consistent with reports that these compounds are

inhibitors of cytochrome P450 and with the reduced sensitivity of mammalian cytochrome P450 to **fluconazole** as compared with ketoconazole. **PubMed Abstract**

Latrille F et al; Res Commun Chem Pathol Pharmacol 64 (1): 173-6 (1989)

▸ **from HSDB**

/ALTERNATIVE and IN VITRO TESTS/ The effect of ketoconazole on Ca(2+) signaling in Madin-Darby canine kidney (MDCK) cells was investigated by using **fura-2** as a Ca(2+) probe. Ketoconazole evoked increases in cytosolic free Ca(2+) concentration ([Ca(2+)](i)) concentration dependently. The response was decreased by external Ca(2+) removal. In Ca(2+)-free medium, pretreatment with ketoconazole abolished the [Ca(2+)](i) rise induced by **thapsigargin**, an inhibitor of the endoplasmic reticulum Ca(2+) pump. Addition of 3 mM Ca(2+) induced a significant [Ca(2+)](i) rise after preincubation with 150 microM ketoconazole in Ca(2+)-free medium. Pretreatment with **aristolochic acid** (40 microM) to inhibit phospholipase A(2) inhibited the 150-microM-ketoconazole-induced internal Ca(2+) release by 37%, but inhibition of phospholipase C with 1-(6-((17beta-3-methoxyestra-1,3, 5(10)-trien-17-yl)amino)hexyl)-1H-pyrrole-2,5-dione (**U73122**) (2 microM) had no effect. Collectively, we found that ketoconazole increases [Ca(2+)](i) in MDCK cells by releasing Ca(2+) from **thapsigargin**-sensitive pools in a manner independent of the production of **inositol**-1,4,5-**trisphosphate**, followed by Ca(2+) influx from the external space. **PubMed Abstract**

Jan C, Tseng C; Biochem Pharmacol 59 (8): 947-51 (2000)

▸ **from HSDB**

/VETERINARY CASE REPORTS/ A Chinese shar pei with a 2 yr history of episodic fever, lethargy, and shifting lameness was presumptively diagnosed with familial shar pei fever but had never been treated for the syndrome. After being presented for a superficial pyoderma with possible dermatophyte coinfection, treatment with a cephalosporin and ketoconazole were prescribed. One wk later, **colchicine** was initiated for familial shar pei fever using cautious dose escalation. Nevertheless, gastrointestinal toxicity, skeletal muscle myopathy, and hepatotoxicity developed within 2 wk. Abrupt resolution of gastrointestinal toxicity and myopathy followed drug withdrawal. However, escalating liver enzyme activity and hyperbilirubinemia led to liver biopsy to rule out an antecedent hepatopathy. Biopsy characterized canalicular cholestasis and **colchicine**-associated metaphase arrest and ring mitoses reflecting repression of mitotic spindle formation. Signs of illness completely resolved 3 mo after drug discontinuation. Although avoidable adverse interactions between ketoconazole and drugs reliant on cytochrome oxidase biotransformation and/or drug efflux mediated by multiple drug-resistant transporters are well documented in humans, these are rarely reported in veterinary patients. This case exemplifies an important and avoidable ketoconazole/**colchicine** drug interaction from which the patient completely recovered. The dog tested negative for the canine MDR1 loss of function mutation that also might potentiate **colchicine** toxicity. **PubMed Abstract**

McAlister A et al; J Am Anim Hosp Assoc 50 (6): 417-423 (2014)

▸ **from HSDB**

12.1.13 Non-Human Toxicity Values

LD50 Rats oral 166 mg/kg

Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 2191

▸ **from HSDB**

LD50 Rats iv 86 mg/kg

Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 2191

▸ **from HSDB**

LD50 Mice oral 618 mg/kg

Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 2191

▸ **from HSDB**

LD50 Mice iv 41,500 ug/kg

Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 2191

▸ **from HSDB**

LD50 Dog oral 178 mg/kg

Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 2191

▸ **from HSDB**

12.1.14 Ecotoxicity Values

EC50; Species: Daphnia magna (**Water** Flea) age <24 hr neonate; Conditions: freshwater, static, 20 deg C; Concentration: 8100 ug/L for 24 hr (95% confidence interval: 4600-10800 ug/L); Effect: intoxication, immobilization /100% purity/

*Haeba MH et al; Environ Sci Pollut Res 15 (3): 222-227 (2008) as cited in the ECOTOX database. Available from, as of October 5, 2014: **http://cfpub.epa.gov/ecotox/quick_query.htm***

from HSDB

EC50; Species: Daphnia magna (**Water** Flea) age <24 hr neonate; Conditions: freshwater, static, 20 deg C; Concentration: 1510 ug/L for 48 hr (95% confidence interval: 1160-1910 ug/L); Effect: intoxication, immobilization /100% purity/

*Haeba MH et al; Environ Sci Pollut Res 15 (3): 222-227 (2008) as cited in the ECOTOX database. Available from, as of October 5, 2014: **http://cfpub.epa.gov/ecotox/quick_query.htm***

from HSDB

12.1.15 Ecotoxicity Excerpts

/AQUATIC SPECIES/ The use of N-substituted imidazoles is widespread, and **imidazole** and triazole fungicides have been detected in the aquatic environment and shown to bioaccumulate in fish. ...The effects of the model **imidazole**, ketoconazole, on drug-metabolizing cytochrome P450 (CYP) forms /were investigated;/ ... focused on cytochrome P4501A (CYP1A) and cytochrome P4503A (CYP3A) expression and activities in juvenile rainbow trout and in adult killifish. The CYP1A expression (mRNA, protein) and activity was induced in rainbow trout, whereas in killifish no effect of ketoconazole on CYP1A protein expression was observed. A biphasic dose-response relationship was observed between ketoconazole exposure and hepatic CYP1A-mediated **ethoxyresorufin** O-deethylase (EROD) activity in rainbow trout in vitro and in vivo, implying that higher doses of ketoconazole inhibit CYP1A activities. Slight induction of CYP3A protein levels was observed in rainbow trout exposed in vivo to ketoconazole. However, the CYP3A-mediated benzyloxy-4-[trifluoromethyl]-coumarin (BFC) O-debenzyloxylase activity was reduced in rainbow trout and killifish treated with ketoconazole. In vitro inhibition studies confirmed that ketoconazole was a potent inhibitor of both CYP3A and CYP1A enzyme activities in these species. This study showed that ketoconazole induced CYP1A and CYP3A expression in rainbow trout. However, the most pronounced effect of ketoconazole was a 60 to 90% decrease in CYP3A catalytic activities in rainbow trout and in killifish. **PubMed Abstract**

Hegelund T et al; Environ Toxicol Chem 23 (5): 1326-34 (2004)

from HSDB

/AQUATIC SPECIES/ This study focuses on effects of two classes of xenobiotics, **azole** fungicides and xenoestrogens, both of which have been detected in the aquatic environment. ...Rainbow trout (Oncorhynchus mykiss) /were exposed/ to two different pharmaceutical representatives of these two classes, such as the **imidazole** ketoconazole and the synthetic estrogen analogue, **17alpha-ethynylestradiol** (EE(2)). Juvenile rainbow trout were i.p. injected with a single low dose of EE(2) (2.5 ug/kg), alone or in combination with ketoconazole (100 mg/kg). Hepatic microsomal CYP1A and CYP3A protein expressions were analyzed in Western blots using polyclonal antibodies (PAb) and enhanced cheminoluminescence. CYP1A activities were analyzed using the **ethoxyresorufin**-O-deethylase (EROD) assay and CYP3A activities were analyzed using the benzyloxy-4-[trifluoromethyl]-coumarin-O-debenzyloxylase (BFCOD) assay. Plasma vitellogenin (vtg) and sex steroid hormones (i.e. **17beta-estradiol**, **testosterone** and **11-keto-testosterone**) were analyzed using commercially available ELISA-kits. The vtg mRNA expression was analyzed using quantitative (Q)-PCR. The dose of EE(2) selected had little or no effect on the estrogen receptor (ER) mediated vtg induction. However, in combination with ketoconazole this threshold-dose of EE(2) resulted in significantly elevated plasma vtg levels, 6 days post injection. Exposure to ketoconazole resulted in up to nine-fold induction of CYP1A after 3 days. However, this nine-fold induction was not reflected on the CYP1A catalytic activity, where exposure to ketoconazole resulted only in a two-fold increase in activity. Ketoconazole increased CYP3A protein levels 1.5-fold and decreased BFCOD activities by 80% at days 3 and 6. Treatment with ketoconazole and EE(2) alone and in combination had no significant effect on sex steroid hormones, compared to vehicle-treated fish. This study demonstrates that exposure to ketoconazole compromises the function of key enzymes involved in metabolic clearance of xenobiotics and steroids, and increases the sensitivity to EE(2) exposure in juvenile rainbow trout. **PubMed Abstract**

Hasselberg L et al; Aquat Toxicol 86 (2): 256-64 (2008)

from HSDB

/AQUATIC SPECIES/ An understanding of the effects of toxic mixtures of endocrine disrupting chemicals (EDCs) on aquatic organisms is challenging as these organisms are exposed to multiple classes of contaminants in their natural habitat. The aim of the present study was to evaluate the interactions of two classes of EDCs, **17beta-estradiol** (E2) and ketoconazole (KTC), on endocrine function in male goldfish (Carassius auratus), including vitellogenesis, metabolic capability and serum steroid synthesis. Changes in vitellogenin (VTG) concentration, liver **7-ethoxyresorufin**-O-deethylase (EROD) activity and circulating serum E2 level were examined. The expression of related genes was also determined using quantitative real-time polymerase chain reaction. Exposure to E2 caused a significant increase in VTG concentrations which corresponded with the gene expression of VTG and estrogen receptor (ER) in males, which were further elevated after combined exposure to E2 and KTC, indicative of a synergetic relationship. Exposure to E2 also resulted in a distinct increase in serum steroid biosynthesis and associated cytochrome P450 (CYP) aromatase expression after 10 days. However, these changes were inhibited by the presence of KTC, which acted as a steroidogenic inhibitor in fish. Moreover, KTC significantly decreased liver EROD activity and increased the related gene expression of CYP1A. However, these KTC-mediated metabolic reactions in goldfish were up-regulated following exposure to KTC in combination with E2. These findings reveal complex interactions on endocrine functions in male goldfish when exposed to multiple contaminations and may provide a better understanding of the effects of toxic mixtures. **PubMed Abstract**

Yan Z et al; Aquat Toxicol 132-133: 9-25 (2013)

from HSDB

/AQUATIC SPECIES/ Ketoconazole (KTC) is a model pharmaceutical representing **imidazole** and triazole pesticides, which inhibit fungal growth through blocking a cytochrome P450 (CYP)-mediated step in **ergosterol** biosynthesis. Several of these fungicides have been shown to be reversible inhibitors of CYPs in vertebrates (primarily mammals), including CYP isoforms involved in the pathway that converts **cholesterol** to active sex steroids. In these studies, we assessed the effects of KTC on

aspects of steroidogenesis and reproductive function in the fathead minnow (Pimephales promelas). Exposure of spawning adults to the fungicide for 21 days significantly decreased egg production at a **water** concentration as low as 25 ug/L. Despite evidence of reduced ex vivo **testosterone** production by gonads from KTC-exposed fathead minnows, circulating plasma concentrations of sex steroids (**testosterone**, **17beta-estradiol**) were not affected. Exposure to KTC caused an increase in the gonadosomatic index in both sexes and, in males, the fungicide caused a marked proliferation of interstitial (Leydig) cells. In addition, mRNA transcripts for two key steroidogenic enzymes, cytochrome P450 side-chain cleavage (CYP11A) and cytochrome P450 c17a hydroxylase/17,20 lyase (CYP17), were elevated by exposure to KTC. Both the changes in transcript levels and proliferation of gonad tissue represent potential adaptive or compensatory responses to impaired steroidogenic capacity. Overall our data indicate that, although KTC does adversely affect steroidogenesis and reproduction in the fathead minnow, the fish can compensate to some degree to mitigate effects of the fungicide. This has important implications for the interpretation of data from tests with endocrine-active chemicals.

Ankley GT et al; Environ Toxicol Chem 26 (6): 1214-23 (2007)

▸ from HSDB

/AQUATIC SPECIES/ Pollution-induced endocrine disruption in vertebrates and invertebrates is a worldwide environmental problem, but relatively little is known about effects of endocrine disrupting compounds (EDCs) in planktonic crustaceans (including Daphnia magna). Aims of the present study were to investigate acute 48 hr toxicity and sub-chronic (4-6 days) and chronic (21 days) effects of selected EDCs in D. magna. ...Both traditional endpoints as well as other parameters such as sex determination, maturation, molting or embryogenesis /have been investigated/ in order to evaluate the sensitivity and possible use of these endpoints in ecological risk assessment. ...Effects of four model EDCs (**vinclozolin**, **flutamide**, ketoconazole and **dicofol**) on D. magna /were studied/ using (i) an acute 48 hr immobilization assay, (ii) a sub-chronic, 4-6 day assay evaluating development and the sex ratio of neonates, and (iii) a chronic, 21 day assay studying number of neonates, sex of neonates, molting frequency, day of maturation and the growth of maternal organisms. Acute EC50 values in the 48 hr immobilization test were as follows (mg/L): **dicofol** 0.2, ketoconazole 1.5, **flutamide** 2.7, **vinclozolin** >3. Short-term, 4-6 day assays with sublethal concentrations showed that the sex ratio in Daphnia was modulated by **vinclozolin** (decreased number of neonate males at 1 mg/L) and **dicofol** (increase in males at 0.1 mg/L). **Flutamide** (up to 1 mg/L) had no effect on the sex of neonates, but inhibited embryonic development at certain stages during chronic assay, resulting in abortions. Ketoconazole had no significant effects on the studied processes up to 1 mg/L. Sex ratio modulations by some chemicals (**vinclozolin** and **dicofol**) corresponded to the known action of these compounds in vertebrates (i.e. anti-androgenicity and anti-oestrogenicity, respectively). /The/ study revealed that some chemicals known to affect steroid-regulated processes in vertebrates can also affect sublethal endpoints (e.g. embryonic sex determination and/or reproduction) in invertebrates such as D. magna. A series of model vertebrate endocrine disrupters affected various sub-chronic and chronic parameters in D. magna including several endpoints that have not been previously studied in detail (such as sex determination in neonates, embryogenesis, molting and maturation). Evaluations of traditional reproduction parameters (obtained from the 21 day chronic assay). as well as the results from a rapid, 4-6 day, sub-chronic assay provide complementary information on non-lethal effects of suspected organic endocrine disrupters. RECOMMENDATIONS AND PERSPECTIVES: It seems that there are analogies between vertebrates and invertebrates in toxicity mechanisms and in vivo effects of endocrine disruptors. However, general physiological status of organisms may also indirectly affect endpoints that are traditionally considered 'hormone regulated' (especially at higher effective concentrations as observed in this study) and these factors should be carefully considered. Further research of D. magna physiology and comparative studies with various EDCs will help to understand mechanisms of action as well as ecological risks of EDCs in the environment. **PubMed Abstract**

Haeba MH et al; Environ Sci Pollut Res Int 15 (3): 222-7 (2008)

▸ from HSDB

/AQUATIC SPECIES/ This study evaluated changes in the expression of steroidogenesis-related genes in male fathead minnows exposed to ketoconazole (KTC) or **vinclozolin** (VZ) for 21 days. ...Variation in the relative abundance of steroidogenesis-related gene transcripts in the gonads of male and female fathead minnows as a function of age, gonad development, and spawning status, independent of EAC exposure /was examined/. Gonadal expression of several genes varied with age and/or gonadal somatic index in either males or females. However, with the exception of aromatase, steroidogenesis-related gene expression did not vary with spawning status. Following the baseline experiments, expression of the selected genes in male fathead minnows exposed to KTC or VZ was evaluated in the context of effects observed at higher levels of organization. Exposure to KTC elicited changes in gene transcription that were consistent with an apparent compensatory response to the chemical's anticipated direct inhibition of steroidogenic enzyme activity. Exposure to VZ, an antiandrogen expected to indirectly impact steroidogenesis, increased pituitary expression of follicle-stimulating hormone beta-subunit as well as testis expression of 20beta-hydroxysteroid dehydrogenase and luteinizing hormone receptor transcripts. Results of this study contribute to ongoing research aimed at understanding responses of the teleost hypothalamic-pituitary-gonadal axis to different types of **EACs** and how changes in molecular endpoints translate into apical outcomes reflective of either adverse effect or compensation.

Villenueve DL et al; Toxicol Sci 98 (2): 395-407 (2007)

▸ from HSDB

/AQUATIC SPECIES/ The objective of this study was to evaluate temporal effects of the model steroidogenesis inhibitor ketoconazole (KTC) on aspects of reproductive endocrine function controlled by the hypothalamic-pituitary-gonadal (HPG) axis in the fathead minnow (Pimephales promelas). Ketoconazole inhibits the activity of two cytochrome P450s (CYPs) key to sex steroid production in vertebrates, CYP11a (**cholesterol** side chain cleavage) and CYP17 (c17a-hydroxylase/17, 20-lyase). Sexually mature fish were exposed to **water**-borne KTC (30 or 300 ug/L) in a flow-through system for up to 8 d, following which animals were allowed to recover in clean **water**. Fish were sampled after 1, 4 and 8 d of exposure, and after 1, 8 and 16 days of recovery. A shorter-term time-course experiment also was conducted in which females were sampled on seven occasions during a 12 hr KTC exposure. Ketoconazole consistently depressed ex vivo gonadal synthesis of **testosterone** (T) in both sexes, and **17beta-estradiol** (E2) in females during both exposure and recovery phases of the time-course studies. Effects on ex vivo steroidogenesis in females occurred within as little as 1 hr of exposure. Plasma concentrations of T in males and E2 in females also were depressed by exposure to KTC, but these decreases did not persist to the same degree as observed for the ex vivo effects. In females, after decreases within 12 hr, plasma E2 concentrations were similar to (or greater than) controls at 24 hr of exposure, while in males, plasma T returned to levels comparable to controls within 1 day of

cessation of KTC exposure. The discrepancy between the ex vivo and in vivo data at later stages in the test is consistent with some type of compensatory response to KTC in fish. However, we were unable to ascertain the mechanistic basis for such a response. For example, although a number of genes related to steroid synthesis (e.g., cyp11a, cyp17) were up-regulated in the gonads of both males and females during the exposure and early recovery phases of the experiment, this did not seem to account for the resurgence in plasma steroid concentrations in KTC-exposed fish. ...

Ankley GT et al; Aquat Toxicol 114-115: 88-95 (2012)

from HSDB

/AQUATIC SPECIES/ Effects of two model **imidazole**-type fungicides, **prochloraz** (PCZ) and ketoconazole (KTC), on the hypothalamic-pituitary-gonadal (HPG) axis of the Japanese medaka (Oryzias latipe) were examined by use of real time PCR (RT-PCR) array. Fourteen-week-old Japanese medaka were exposed for seven days to concentrations of PCZ or KTC from 3.0 to 300 ug/L. Exposure to KTC or PCZ caused significant reduction of fecundity of Japanese medaka and down-regulated expression of estrogen receptor (ER)-a and egg precursors in livers of males and females. However, PCZ was more potent than KTC both in modulating transcription and causing lesser fecundity. Exposure to nominal 30 ug PCZ/L resulted in 50% less fecundity and significant down-regulation of vitellogenin II expression, but KTC did not cause such effects at this concentration. Exposure to PCZ caused a compensatory up-regulation in cytochrome P450 c17ahydroxylase, 17,20-lyase (CYP17) and aromatase (CYP19) expression in the ovary, while KTC did not. Furthermore, the ecologically relevant end point, fecundity was log-log related to mRNA level of six genes in livers of females.

Zhang X et al; Environ Sci Technol 42 (17): 6762-69 (2008)

from HSDB

12.1.16 Populations at Special Risk

Ketoconazole is contraindicated in women of childbearing potential unless effective forms of contraception are employed.

*Health Canada; Product Monograph for Teva-Ketoconazole (Ketoconazole Tablets USP), Drug Identification Number (DIN): 02231061, p2 (Revision date: March 4, 2014). Available from, as of November 12, 2014: **http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng***

from HSDB

The use of **Nizoral** Tablets is contraindicated in patients with acute or chronic liver disease.

*NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of November 11, 2014: **http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465***

from HSDB

12.2 Ecological Information

12.2.1 ICSC Environmental Data

The substance is very toxic to aquatic organisms. It is strongly advised not to let the chemical enter into the environment.

from ILO International Chemical Safety Cards (ICSC)

12.2.2 Environmental Fate/Exposure Summary

Ketoconazole's production and administration as an antifungal agent may result in its release to the environment through various waste streams. If released to air, an estimated vapor pressure of 6.4X10-14 mm Hg at 25 deg C indicates ketoconazole will exist solely in the particulate phase in the atmosphere. Particulate-phase ketoconazole will be removed from the atmosphere by wet and dry deposition. Ketoconazole contains chromophores that absorb at wavelengths >290 nm and, therefore, may be susceptible to direct photolysis by sunlight. If released to soil, ketoconazole is expected to have slight mobility based upon an estimated Koc of 3,000. An estimated pKa of 3.96 indicates that this compound will exist partially in the cation form in the environment and cations generally adsorb more strongly to soils containing organic **carbon** and clay than their neutral counterparts. Volatilization of the neutral species from moist soil surfaces is not expected to be an important fate process based upon an estimated Henry's Law constant of 5.6X10-20 atm-cu m/mole. Ketoconazole is not expected to volatilize from dry soil surfaces based upon its vapor pressure. Ketoconazole was found to be biodegraded under sewage treatment plant conditions, suggesting biodegradation may be an important environmental fate process in soil or **water**. If released into **water**, ketoconazole is expected to adsorb to suspended solids and sediment based upon the estimated Koc. Volatilization from **water** surfaces is not expected to be an important fate process based upon this compound's estimated Henry's Law constant. An estimated BCF of 340 suggests the potential for bioconcentration in aquatic organisms is high. Hydrolysis is not expected to be an important environmental fate process since this compound lacks functional groups that hydrolyze under environmental conditions (pH 5 to 9). Occupational exposure to ketoconazole may occur through inhalation and dermal contact with this compound at workplaces where ketoconazole is produced or used. Exposure to ketoconazole among the general population may be limited to those administered the drug. (SRC)

from HSDB

12.2.3 Artificial Pollution Sources

Ketoconazole's production and administration as an antifungal agent(1) may result in its release to the environment through various waste streams(SRC).

(1) O'Neil MJ, ed; The Merck Index. 15th ed., Cambridge, UK: Royal Society of Chemistry, p. 983 (2013)

from HSDB

12.2.4 Environmental Fate

TERRESTRIAL FATE: Based on a classification scheme(1), an estimated Koc value of 3,000(SRC), determined from a log Kow of 4.34(2) and a regression-derived equation(3), indicates that ketoconazole is expected to have slight mobility in soil(SRC). The estimated pKa of 3.96(4) indicates that this compound will exist partially in the cation form in the environment and cations generally adsorb more strongly to soils containing organic carbon and clay than their neutral counterparts(5). Volatilization of ketoconazole from moist soil surfaces is not expected to be an important fate process(SRC) given an estimated Henry's Law constant of 5.6X10-20 atm-cu m/mole(SRC), using a fragment constant estimation method(4). Ketoconazole is not expected to volatilize from dry soil surfaces(SRC) based upon an estimated vapor pressure of 6.4X10-14 mm Hg at 25 deg C(SRC), determined from a fragment constant method(3). Ketoconazole was found to be biodegraded under sewage treatment plant conditions(5), suggesting biodegradation may be an important environmental fate process in soil(SRC).

*(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) Hansch C et al; Exploring QSAR. Hydrophobic, Electronic, and Steric Constants. ACS Prof Ref Book. Heller SR, consult. ed., Washington, DC: Amer Chem Soc p. 186 (1995) (3) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012. Available from, as of Aug 27, 2014: **http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm** (4) ChemSpider; Ketoconazole (65277-42-1). London, UK: Royal Chemical Society. Available from, as of Aug 27, 2014: **http://www.chemspider.com/Search.aspx** (5) Doucette WJ; pp. 141-188 in Handbook of Property Estimation Methods for Chemicals. Boethling RS, Mackay D, eds. Boca Raton, FL: Lewis Publ (2000) (6) Peng X et al; Sci Total Environ 426: 311-7 (2012)*

from HSDB

AQUATIC FATE: Based on a classification scheme(1), an estimated Koc value of 3,000(SRC), determined from a log Kow of 4.34(2) and a regression-derived equation(3), indicates that ketoconazole is expected to adsorb to suspended solids and sediment(SRC). Volatilization of the neutral species from water surfaces is not expected(4) based upon an estimated Henry's Law constant of 5.6X10-20 atm-cu m/mole(SRC), developed using a fragment constant estimation method(5). According to a classification scheme(6), an estimated BCF of 340(SRC), from its log Kow(2) and a regression-derived equation(3), suggests the potential for bioconcentration in aquatic organisms is high(SRC). Ketoconazole was found to be biodegraded under sewage treatment plant conditions(7), suggesting biodegradation may be an important environmental fate process in water(SRC).

*(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) Hansch C et al; Exploring QSAR. Hydrophobic, Electronic, and Steric Constants. ACS Prof Ref Book. Heller SR, consult. ed., Washington, DC: Amer Chem Soc p. 186 (1995) (3) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012. Available from, as of Aug 27, 2014: **http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm** (4) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 15-1 to 15-29 (1990) (5) ChemSpider; Ketoconazole (65277-42-1). London, UK: Royal Chemical Society. Available from, as of Aug 27, 2014: **http://www.chemspider.com/Search.aspx** (6) Franke C et al; Chemosphere 29: 1501-14 (1994) (7) Peng X et al; Sci Total Environ 426: 311-7 (2012)*

from HSDB

ATMOSPHERIC FATE: According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere(1), ketoconazole, which has an estimated vapor pressure of 6.4X10-14 mm Hg at 25 deg C(SRC), determined from a fragment constant method(2), is expected to exist solely in the particulate phase in the ambient atmosphere. Particulate-phase ketoconazole may be removed from the air by wet and dry deposition(SRC). Ketoconazole contains chromophores that absorb at wavelengths >290 nm(3) and, therefore, may be susceptible to direct photolysis by sunlight(SRC).

*(1) Bidleman TF; Environ Sci Technol 22: 361-367 (1988) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012. Available from, as of Aug 27, 2014: **http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm** (3) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 8-12 (1990)*

from HSDB

12.2.5 Environmental Biodegradation

AEROBIC: Residue of azole antifungals in the environment is of concern due to the environmental risks and persistence. Distribution, behavior, and fate of frequently used azole antifungal pharmaceuticals were investigated in wastewater at two sewage treatment plants (STPs) in China. Fluconazole, clotrimazole, econazole, ketoconazole, and miconazole were constantly detected at 1-1834 ng/L in the wastewater. The latter four were also ubiquitously detected in sewage sludge. Fluconazole passed through treatment in the STPs and largely remained in the final effluent. On the contrary, biotransformation and sorption to sludge occurred to the other azoles. Ketoconazole was more readily bio-transformed, whereas clotrimazole, econazole, and miconazole were more likely to be adsorbed onto and persisted in sewage sludge. Lipophilicity plays the governing role on adsorption. The highest concentrations in the raw wastewater were observed in winter for the azole pharmaceuticals except for fluconazole. The seasonal difference was smoothed out after treatment in the STPs. PubMed Abstract

Peng X et al; Sci Total Environ 426: 311-7 (2012)

from HSDB

12.2.6 Environmental Abiotic Degradation

Ketoconazole is not expected to undergo hydrolysis in the environment due to the lack of functional groups that hydrolyze under environmental conditions(1). Ketoconazole contains chromophores that absorb at wavelengths >290 nm(1) and, therefore, may be susceptible to direct photolysis by sunlight(SRC).

(1) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 7-4, 7-5, 8-12 (1990)

from HSDB

12.2.7 Environmental Bioconcentration

An estimated BCF of 340 was calculated in fish for ketoconazole(SRC), using a log Kow of 4.34(1) and a regression-derived equation(2). According to a classification scheme(3), this BCF suggests the potential for bioconcentration in aquatic organisms is high(SRC).

*(1) Hansch C et al; Exploring QSAR. Hydrophobic, Electronic, and Steric Constants. ACS Prof Ref Book. Heller SR, consult. ed., Washington, DC: Amer Chem Soc p. 186 (1995) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012. Available from, as of Aug 27, 2014: **http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm/** (3) Franke C et al; Chemosphere 29: 1501-14 (1994)*

from HSDB

12.2.8 Soil Adsorption/Mobility

The Koc of ketoconazole is estimated as 3,000(SRC), using a log Kow of 4.34(1) and a regression-derived equation(2). According to a classification scheme(3), this estimated Koc value suggests that ketoconazole is expected to have slight mobility in soil. The estimated pKa value of 3.96(4) indicates that this compound will exist partially in the cation form in the environment and cations generally adsorb more strongly to soils containing organic carbon and clay than their neutral counterparts(5). Ketoconazole adsorption isotherms (Kd) of 9.7X10+3 L/kg and 8.5X10+3 L/kg were measured in primary sludge and long-age secondary sludge, respectively. Sludge was obtained from 2 wastewater treatment plants that were representative of plants utilized in industrialized countries(6).

*(1) Hansch C et al; Exploring QSAR. Hydrophobic, Electronic, and Steric Constants. ACS Prof Ref Book. Heller SR, consult. ed., Washington, DC: Amer Chem Soc p. 186 (1995) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012. Available from, as of Aug 27, 2014: **http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm** (3) Swann RL et al; Res Rev 85: 17-28 (1983) (4) ChemSpider; Ketoconazole (65277-42-1). London, UK: Royal Chemical Society. Available from, as of Aug 27, 2014: **http://www.chemspider.com/Search.aspx** (5) Doucette WJ; pp. 141-188 in Handbook of Property Estimation Methods for Chemicals. Boethling RS, Mackay D, eds. Boca Raton, FL: Lewis Publ (2000) (6) Horsing M et al; Water Res 45: 4470-4482 (2011)*

from HSDB

12.2.9 Volatilization from Water/Soil

The Henry's Law constant for ketoconazole is estimated as 5.6X10-20 atm-cu m/mole(SRC) using a fragment constant estimation method(1). This Henry's Law constant indicates that ketoconazole is expected to be essentially nonvolatile from water and moist soil surfaces(2). Ketoconazole is not expected to volatilize from dry soil surfaces(SRC) based upon an estimated vapor pressure of 6.4X10-14 mm Hg(SRC), determined from a fragment constant method(3).

*(1) Meylan WM, Howard PH; Environ Toxicol Chem 10: 1283-93 (1991) (2) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 15-1 to 15-29 (1990) (3) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012. Available from, as of Aug 27, 2014: **http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm***

from HSDB

12.2.10 Environmental Water Concentrations

While data specific to ketoconazole were not located(SRC, 2014), the literature suggests that some pharmaceutically active compounds originating from human and veterinary therapy are not eliminated completely in municipal sewage treatment plants and are, therefore, discharged into receiving waters(1). Wastewater treatment processes often were not designed to remove them from the effluent(2). Selected organic waste compounds may be degrading to new and more persistent compounds that may be released instead of or in addition to the parent compound(2).

(1) Heberer T; Tox Lett 131: 5-17 (2002) (2) Koplin DW et al; Environ Sci Toxicol 36: 1202-211 (2002)

from HSDB

12.2.11 Milk Concentrations

EXPERIMENTAL: Ketoconazole has been shown to be excreted in the milk.

*(1) NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet (Revised: March 2014). Available from, as of February 2, 2015: **http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=090660c1-6e6d-457f-adb5-046ddfcd1465***

from HSDB

EXPERIMENTAL: Infant exposure to ketoconazole in human milk was calculated to be 0.4% on average (maximum 1.4%) of those expected from therapeutic doses given directly to infants. ... PubMed Abstract

Moretti ME et al; Am J Obstet Gynecol 173 (5): 1625-6

from HSDB

12.2.12 Probable Routes of Human Exposure

NIOSH (NOES Survey 1981-1983) has statistically estimated that 1,045 workers (620 of these were female) were potentially exposed to ketoconazole in the US(1). Occupational exposure to ketoconazole may occur through inhalation and dermal contact with this compound at workplaces where ketoconazole is produced or used. Exposure to ketoconazole among the general population may be limited to those administered the drug(SRC).

*(1) NIOSH; NOES. National Occupational Exposure Survey conducted from 1981-1983. Estimated numbers of employees potentially exposed to specific agents by 2-digit standard industrial classification (SIC). Available from, as of Aug 25, 2014: **http://www.cdc.gov/noes/***

from HSDB

13 Literature

13.1 Depositor Provided PubMed Citations

from PubChem

13.2 NLM Curated PubMed Citations

from PubChem

13.3 Springer Nature References

from Springer Nature

13.4 Thieme References

from Thieme Chemistry

13.5 Chemical Co-Occurrences in Literature

from PubChem

13.6 Chemical-Disease Co-Occurrences in Literature

from PubChem

13.7 Chemical-Gene Co-Occurrences in Literature

from PubChem

14 Patents

14.1 Depositor-Supplied Patent Identifiers

from PubChem

14.2 FDA Orange Book Patents

Patent	8232276
Expiration	Nov 24, 2020
Applicant	ALMIRALL
Drug Application	N021946 (Prescription Drug: XOLEGEL. Ingredients: KETOCONAZOLE)

from FDA Orange Book

15 Biomolecular Interactions and Pathways

15.1 Protein Bound 3-D Structures

from PDB

View 2 proteins in NCBI Structure

from PubChem

16 Biological Test Results

16.1 BioAssay Results

from PubChem

17 Classification

17.1 Ontologies

17.1.1 MeSH Tree

from MeSH

17.1.2 ChEBI Ontology

from ChEBI

17.1.3 KEGG: Drug

▸ from KEGG

17.1.4 KEGG: USP

▸ from KEGG

17.1.5 KEGG: ATC

▸ from KEGG

17.1.6 KEGG: JP15

▸ from KEGG

17.1.7 KEGG: Drug Classes

from KEGG

17.1.8 WHO ATC Classification System

from WHO ATC

17.1.9 WIPO IPC

from WIPO

17.1.10 ChemIDplus

from ChemIDplus

17.1.11 ChEMBL Target Tree

from ChEMBL

17.1.12 UN GHS Classification

from UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

18 Information Sources

FILTER BY SOURCE ALL SOURCES

1. **ChEBI**
   (2S,4R)-ketoconazole
   http://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:47518
   ChEBI Ontology
   http://www.ebi.ac.uk/chebi/userManualForward.do#ChEBI%20Ontology
2. **Human Metabolome Database (HMDB)**
   Ketoconazole
   http://www.hmdb.ca/metabolites/HMDB0012242
3. **LiverTox**
   Ketoconazole
   https://livertox.nlm.nih.gov/Ketoconazole.htm
4. **NCIt**
   Ketoconazole
   https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&ns=NCI_Thesaurus&code=C605
5. **ChemIDplus**
   Ketoconazole [USAN:USP:INN:BAN:JAN]
   https://chem.nlm.nih.gov/chemidplus/sid/0065277421
   Levoketoconazole [USAN]
   https://chem.nlm.nih.gov/chemidplus/sid/0142128572
   (+)-Ketoconazole
   https://chem.nlm.nih.gov/chemidplus/sid/0142128594
   ChemIDplus Chemical Information Classification
   https://chem.sis.nlm.nih.gov/chemidplus/

6. **EPA DSSTox**

   Ketoconazole, (2S,4R)-
   https://comptox.epa.gov/dashboard/DTXSID60161949

7. **European Chemicals Agency (ECHA)**

   ketoconazole
   https://echa.europa.eu/substance-information/-/substanceinfo/100.059.680

   Ketoconazole
   https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/34735

8. **ILO International Chemical Safety Cards (ICSC)**

   KETOCONAZOLE
   http://www.ilo.org/dyn/icsc/showcard.display?p_version=2&p_card_id=1700

9. **The National Institute for Occupational Safety and Health (NIOSH)**

   Piperazine, 1-acetyl-4-(4-((2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy)phenyl)-, cis-
   https://www.cdc.gov/niosh-rtecs/TK78BB6C.html

10. **ClinicalTrials.gov**

    Ketoconazole
    https://clinicaltrials.gov/

11. **DailyMed**

    KETOCONAZOLE
    https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=KETOCONAZOLE

12. **EU Clinical Trials Register**

    https://www.clinicaltrialsregister.eu/

13. **EU Community Register of Medicinal Products**

    ketoconazole
    https://ec.europa.eu/health/documents/community-register/html/ho25029.htm

    ketoconazole
    https://ec.europa.eu/health/documents/community-register/html/h965.htm

    ketoconazole
    https://ec.europa.eu/health/documents/community-register/html/o1857.htm

    ketoconazole
    https://ec.europa.eu/health/documents/community-register/html/o1031.htm

    ketoconazole
    https://ec.europa.eu/health/documents/community-register/html/o965.htm

14. **European Medicines Agency (EMA)**

    Ketoconazole HRA
    https://www.ema.europa.eu/en/medicines/human/EPAR/ketoconazole-hra

    Ketoconazole
    https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu312965

    Lentiviral vector carrying the Fanconi anaemia-A (FANCA) gene
    https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu310822

    N-{[(5S)-3-(3-fluoro-4-thiomorpholin-4-ylphenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide
    https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu311897

    Antisense oligonucleotide targeting the USH2A gene
    https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171853

    Ketoconazole
    https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171857

    (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6''-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxo-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3''-indole]-5'-carboxamide mono(4-methylbenzenesulfonate) monohydrate
    https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171847

    Poly-cyclodextrin-bis-cysteine-PEG3400-camptothecin-conjugate
    https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171860

    Patidegib
    https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3181998

    Allogeneic donor-derived ex-vivo expanded T lymphocytes transduced with a retroviral vector containing inducible caspase 9 and truncated CD19
    https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3161674

    pentosan polysulfate sodium
    https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3161663

    Modified messenger ribonucleic acid encoding human ornithine transcarbamylase enzyme encapsulated into lipid nanoparticles
    https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171867

    Autologous adult bone marrow-derived non-expanded CD133+ haematopoietic stem cells
    https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171862

    Estetrol
    https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171865

    Human normal immunoglobulin
    https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171866

    rituximab
    https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171869

    Doxorubicin (administered after synthetic double-stranded siRNA oligonucleotide directed against claudin-5 complexed with polyethyleneimine)
    https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3121006

    Synthetic double-stranded siRNA oligonucleotide directed against claudin-5 complexed with polyethyleneimine (prior to administration of doxorubicin)
    https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3121065

    20% Intravenous fat emulsion consisting of 20% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, and water for injection
    https://www.ema.europa.eu/en/node/6362

15. **WHO ATC**

    https://www.whocc.no/atc/

    ATC Code
    https://www.whocc.no/atc_ddd_index/

16. **EU REGULATION (EC) No 1272/2008**
ketoconazole;1-[4-[4-[[(2SR,4RS)-2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)...
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_.2018.115.01.0001.01.ENG

17. **Hazardous Chemical Information System (HCIS), Safe Work Australia**
ketoconazole
http://hcis.safeworkaustralia.gov.au/HazardousChemical/Details?chemicalID=2715

18. **HSDB**
KETOCONAZOLE
https://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+65277-42-1

19. **FDA Medication Guides**
Nizoral
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=medguide.page

20. **FDA Orange Book**
Patent:8232276
https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm

21. **FDA/SPL Indexing Data**
2DJ8R0NT7K
https://www.fda.gov/ForIndustry/DataStandards/SubstanceRegistrationSystem-UniqueIngredientIdentifierUNII/

22. **MassBank of North America (MoNA)**
Ketoconazole
http://mona.fiehnlab.ucdavis.edu/spectra/browse?inchikey=XMAYWYJOQHXEEK-ZEQKJWHPSA-N

23. **PDB**
http://www.rcsb.org/ligand/KLN

24. **SpectraBase**
https://spectrabase.com/spectrum/BE6H5MWVOos
https://spectrabase.com/spectrum/AP8HAqE7AMN
https://spectrabase.com/spectrum/J9LgOVuNJOK

25. **Springer Nature**
https://pubchem.ncbi.nlm.nih.gov/substance/341474354
https://pubchem.ncbi.nlm.nih.gov/substance/341762860

26. **Thieme Chemistry**

27. **Wikipedia**
(2S,4R)-ketoconazole
https://www.wikidata.org/wiki/Q27120779

28. **MeSH**
Ketoconazole
https://www.ncbi.nlm.nih.gov/mesh/68007654
MeSH Tree
http://www.nlm.nih.gov/mesh/meshhome.html
Cytochrome P-450 CYP3A Inhibitors
https://www.ncbi.nlm.nih.gov/mesh/68065692
Antifungal Agents
https://www.ncbi.nlm.nih.gov/mesh/68000935
14-alpha Demethylase Inhibitors
https://www.ncbi.nlm.nih.gov/mesh/68058888

29. **PubChem**
https://pubchem.ncbi.nlm.nih.gov

30. **KEGG**
Therapeutic category of drugs in Japan
http://www.genome.jp/kegg-bin/get_htext?br08301.keg
USP drug classification
http://www.genome.jp/kegg-bin/get_htext?br08302.keg
Anatomical Therapeutic Chemical (ATC) classification
http://www.genome.jp/kegg-bin/get_htext?br08303.keg
Drugs listed in the Japanese Pharmacopoeia
http://www.genome.jp/kegg-bin/get_htext?br08311.keg
Drug Classes
http://www.genome.jp/kegg-bin/get_htext?br08330.keg

31. **WIPO**
International Patent Classification
http://www.wipo.int/classifications/ipc/

32. **UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS)**
GHS Classification Tree
http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html

33. **ChEMBL**
Target Tree
https://www.ebi.ac.uk/chembl/target/browser

34. **NCBI**
https://www.ncbi.nlm.nih.gov/projects/linkout